THE ROLE OF INFLAMMATION IN ATHEROGENESIS AND IN GUIDING THERAPY OF ATHEROSCLEROSIS*

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ABSTRACT

Investigations into the pathology of coronary heart disease have established inflammation as a major factor. Inflammation contributes to the entire spectrum of the coronary disease process, affording multiple opportunities for intervention. C-reactive protein (CRP), a marker of systemic inflammation, has emerged as a particularly promising tool for assessing risk and response to risk-reducing therapy. Lipid-lowering therapy reduces inflammation in animals and levels of CRP in humans.


Numerous clinical and preclinical studies have clearly established inflammation as a major contributor to atherogenesis and its clinical sequelae. Inflammation plays a role in virtually every stage of development and evolution of coronary disease and associated clinical events. C-reactive protein (CRP), a biomarker of systemic inflammation, has emerged as a useful means of assessing coronary risk and perhaps guiding therapy, and adds to the prognostic value of current methods of risk assessment such as cholesterol and cholesterol ratios. Lipid-lowering therapy decreases arterial inflammation in animals and decreases CRP levels in humans.

ATHEROGENESIS AND INFLAMMATION

The earliest stages of atheroma formation involve recruitment into the endothelium of mononuclear phagocytes and other leukocytes that normally do not adhere to endothelium. These white cells enter the intima and transform their functions from those of well-behaved white cells to cells that express scavenger receptors and lead to modification of lipoproteins and formation of foam cells. The foam cells divide and begin to secrete a number of mediators that perpetuate the inflammatory process.

Over the past 12 years, several molecular mediators responsible for various steps in the atherogenic process have been identified. The mediators include vascular cell adhesion molecule-1 (VCAM-1). Inhibition of VCAM-1 delays development of atherosclerotic lesions in animal models. Monocyte chemoattractant protein-1 plays a key role in the induction of leukocyte migration into the arterial wall and transformation of leukocytes into tissue macrophages and formation of foam cells. Macrophage colony-stimulating factor (MCSF) mediates monocyte division and activation and induction of scavenger receptors. Macrophage colony stimulating factor is overexpressed in atherosclerotic plaque and has been shown in gene interruption studies in mice to be a key player in the early stages of the atherosclerotic process.

Inflammation also plays a central role in the thrombotic complications of atherosclerosis, the events that bring many patients to the attention of physicians. Disruption of atherosclerotic plaque results...
in a nidus for the thrombus. One of the key advances in understanding the pathophysiology of acute coronary syndromes has been the recognition that certain plaques are vulnerable or at high risk for rupture.

Inflammation's link to thrombosis begins with the fibrous cap that covers the atherosclerotic plaque. When the cap of an unstable plaque breaks, blood and its coagulation factors come into contact with the lesion's highly thrombogenic lipid core, initiating a thrombotic event.

Interstitial collagen is the major determinant of the integrity of an atherosclerotic plaque's fibrous cap. T-lymphocytes recruited from the blood into the plaque secrete mediators that turn off smooth muscle cells' ability to make the new collagen necessary to repair and maintain the all-important fibrous cap. Inflammatory cells also secrete a variety of proteinases that attack the collagen molecule, which ordinarily is biochemically very stable. As the collagen degrades, the fibrous cap weakens and becomes susceptible to rupture and subsequent thrombus formation1 (Figure 1).

The thrombogenicity of plaque depends largely to tissue factor, which appears to be the molecular trigger for increased coagulability in plaque. The biologic switch for tissue factor is CD40 ligand, which induces tissue factor expression in monocyte-derived macrophages.2

Lipid lowering can modify the inflammation-driven process that leads to plaque rupture and thrombosis. Animals fed a high-cholesterol diet develop atherosclerotic lesions that have features of vulnerable, high-risk human atherosclerotic plaque. In inflammatory cells in the intima, expression of collagenase, the enzyme that degrades collagen in the fibrous plaque, correlates with a low level of collagen within a lesion. When the animals receive prolonged lipid-lowering therapy, marked changes occur in the lesions. The changes include decreased inflammation, abolition of collagenase expression, and an increase in the collagen content of lesions.

Lipid lowering stabilizes the plaque, we believe, by inhibiting the inflammatory process that leads to plaque weakening and increased plaque thrombogenicity. Further evidence in support of this position comes from studies showing that experimental atheroma overexpress tissue factor. Following lipid-lowering therapy, tissue factor and associated thrombogenicity decreased.4

Sampling peripheral blood for the presence of inflammatory cytokines, or acute-phase reactants, can indicate whether observations from studies involving animals and test tubes apply to humans. The inflammatory cascade begins with the release of proinflammatory cytokines in response to an inciting factor, such as modified CRP. The first wave of proinflammatory cytokines, which includes interleukin (IL)-1 and tumor necrosis factor-alpha, elicits a second wave of cytokines in an amplification loop (Figure 2).

The messenger cytokine IL-6 travels to the liver and induces a change in protein expression from the housekeeping variety, such as albumin, to expression of acute-phase proteins involved in host defense and response to stress. The liver then pours out acute-phase proteins, such as CRP and serum amyloid A, which can be measured in the circulation. Thus, a clinical window can be opened onto the inflammatory process that cannot be seen in humans.

EMERGING CLINICAL ROLE OF C-REACTIVE PROTEIN

C-reactive protein is accumulating scientific currency as a potential clinical marker for assessing coronary risk. Over the past 5 years, my colleague, Dr Paul Ridker, has put CRP on the map as a means of identifying individuals who may require intensive therapy. At the 1997 American Heart Association Scientific Sessions,

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**Figure 1. Inflammation Sets the Stage for the Acute Coronary Syndromes**

IFN-γ = interferon gamma; IL-1 = interleukin 1; TNF-α = tumor necrosis factor-alpha; MCP-1 = monocyte chemoattractant protein-1; M-CSF = macrophage colony-stimulating factor.

Dr. Ridker presented data on Physicians Health Study participants who were stratified into quartiles according to their CRP levels. Participants were healthy individuals whose CRP levels were within the normal range. Yet, even normal higher CRP levels correlated with a higher prospective risk of acute myocardial infarction.

Over the past 5 years, 17 concordant clinical trials have shown that CRP prospectively correlates with the risk of coronary heart disease, stroke, peripheral vascular disease, and a variety of other clinical endpoints. Most recently, Dr. Ridker demonstrated that CRP adds prognostic value to cholesterol for assessment of coronary risk. The observation emerged from an analysis of CRP and low-density lipoprotein (LDL) cholesterol levels among the 27,000 participants in the Women’s Health Study (WHS), another large population of well individuals. After stratification of the WHS population into CRP and LDL quintiles, CRP proved superior for predicting risk for all cardiovascular events and for coronary heart disease in particular. For the especially meaningful endpoints of death and survival, CRP also appeared to provide better discrimination (Figure 3).

The outcome of the WHS analysis does not mean that LDL should be discarded in favor of CRP as the preeminent predictor of coronary risk. The results told us that combining an inflammatory marker with traditional risk factors can help identify people who are below the median cholesterol level but still at increased risk for coronary events. The addition of an inflammatory marker to the conventional panel of risk assessment tools appears to provide more prognostic information that may guide therapy, a hypothesis that requires prospective evaluation.

C-reactive protein also demonstrated good risk discrimination when applied to the population in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial, a study of lipid-lowering therapy for primary prevention (Table). Individuals who had a high total cholesterol/high-density lipoprotein (HDL) ratio and a CRP level above the median were at increased risk and did well on statin therapy, which also was cost effective, as reflected in the number needed to treat (NNT). In patients with an adverse lipid profile combined with a CRP below the median, statin therapy was clinically effective and cost effective. In patients with a low total cholesterol/HDL ratio and low CRP level, treatment with a statin was not cost effective.

Most intriguing of all was the group that had a low total cholesterol/HDL ratio and elevated CRP. These patients did not meet traditional lipid criteria for increased risk, but they had evidence of systemic inflammation as reflected in CRP levels above the median. This group had an NNT that was indistinguishable from the group who had high cholesterol levels. C-reactive protein identified a high-risk group that would have escaped detection by conventional risk-assessment tools.

**SUMMARY**

Inflammation is integral to the initiation, evolution, and clinical complications of atherosclerosis. Certain inflammatory markers might have value as discriminants of cardiovascular risk, particularly when combined with conventional methods of risk assessment. CRP, in particular, has emerged as a potentially valuable aid for assessing risk, for identifying patients who would be missed by conventional risk assessment, and possibly for guiding therapy. Lipid-lowering therapy appears to stabilize vulnerable atherosclerotic plaque by reducing inflammation.

**REFERENCES**