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eventy years ago, investigators collaborating in the labora-
tory of Attilio Maseri made the observation that plasma levels of the inflammatory biomarkers C-reactive protein (CRP) and serum amyloid A are elevated in patients with severe unstable angina, and that those with higher levels have worse clinical outcomes. However, as concentrations of CRP, serum amyloid A, and other acute phase reactants increase after ischemia, those initial data as well as comparable findings among postinfarction and chronic ischemia patients could not establish whether basal levels of inflammation were a substantive determinant of future vascular risk. That demonstration required evidence that inflammatory biomarkers such as CRP independently predict future myocardial infarction, stroke, and vascular death in apparently healthy populations free of acute phase stimuli, including cigarette consumption. When my group first presented such evidence in healthy men in 1997 and subsequently confirmed this effect in healthy women, Professor Maseri editorialized that the atherothrombosis epidemic returns to this issue by infusing healthy volunteers with highly purified human CRP. In brief, as Lane et al report in a single-site dose escalation study involving 7 healthy male volunteers, intravenous infusion of a pharmaceutical grade preparation of human CRP in doses ranging from 0.25 to 2.0 mg/kg neither triggered endogenous production of more CRP nor resulted in any significant changes in circulating cytokine levels indicative of an acute systemic inflammatory response. Furthermore, the authors report no changes in neutrophil or platelet counts, nor any changes in heart rate, temperature, or blood pressure. As such, the authors reiterate their previous stance that CRP is unlikely to be a proinflammatory mediator in healthy human adults. Though not studied here, the authors are careful to note that human CRP could well have relevant proinflammatory effects in individuals with existing tissue damage through its role as an activator of the classical complement pathway. This latter rationale is part of the reason why the Pepys laboratory itself has continued to develop direct inhibitors of CRP as a potential treatment for existing cardiovascular disease.

Today, >60 prospective cohort studies confirm the core observation that multiple inflammatory biomarkers, including CRP, serum amyloid A, interleukin (IL)-6, tumor necrosis factor-α, soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, P-selectin, and fibrinogen, all associate with future vascular risk in otherwise healthy populations. Of these inflammatory biomarkers, CRP has become the standard for vascular risk prediction due largely to its ease of measurement and abundance of clinical data; meta-analyses convincingly demonstrate that the magnitude of future cardiovascular risk associated with a 1 SD increase in CRP is at least as large as the risk associated with a comparable 1 SD increase in cholesterol or blood pressure. Despite the remarkable consistency of these data, there has been little in the discussion of inflammation, CRP, and vascular disease that has not, at times, been highly controversial. This is the nature, however, of any paradigm shift where accumulating data challenge an existing set of principles and force consideration of new hypotheses, even if unsettling to the status quo.

Looking back, an early controversy for some investigators was whether CRP was more than a biomarker of inflammation, but also functioned itself as a direct proinflammatory mediator for the atherosclerotic disease process. During this period of investigation, the highly experienced laboratory headed by Mark Pepys consistently cautioned that many of the systemic effects attributed to CRP might be due to endotoxin contamination or to effects secondary to the infusion of bacterial recombinant CRP. In the current issue of Circulation Research, the Pepys laboratory returns to this issue by infusing healthy volunteers with highly purified human CRP. In brief, as Lane et al report in a single-site dose escalation study involving 7 healthy male volunteers, intravenous infusion of a pharmaceutical grade preparation of human CRP in doses ranging from 0.25 to 2.0 mg/kg neither triggered endogenous production of more CRP nor resulted in any significant changes in circulating cytokine levels indicative of an acute systemic inflammatory response. Furthermore, the authors report no changes in neutrophil or platelet counts, nor any changes in heart rate, temperature, or blood pressure. As such, the authors reiterate their previous stance that CRP is unlikely to be a proinflammatory mediator in healthy human adults. Though not studied here, the authors are careful to note that human CRP could well have relevant proinflammatory effects in individuals with existing tissue damage through its role as an activator of the classical complement pathway. This latter rationale is part of the reason why the Pepys laboratory itself has continued to develop direct inhibitors of CRP as a potential treatment for existing cardiovascular disease.

Not addressed in the current article is the fact that the marker versus mediator debate surrounding CRP was for other investigators a diversion away from the more pressing issues of understanding how inflammation as a systemic process influences both the early stages of atherogenesis and the late stages of plaque rupture, occlusive thrombosis, and consequent tissue hypoxia. Even if CRP is only an inflammatory biomarker of vascular risk, it remains a biomarker with at least as much prognostic information as hyperlipidemia or hypertension. Even if downstream CRP elevations are only an acute phase response to upstream disturbance of the IL-1, tumor necrosis factor-α, and IL-6 signaling system, that downstream clinical signal remains crucial to understanding the core biology of inflammation and its role in atherothrombosis. In other words, for investigators not bogged down by the mediator versus marker debate, the relevant issue has not been about targeting...
CRP per se, but about targeting inflammatory pathways more broadly to discern whether such an intervention might have the potential to both treat and prevent cardiovascular disease.8

We now understand that many of the early distinctions between the lipid hypothesis and the inflammation hypothesis may themselves have been artificial. For example, the recognition that cholesterol crystals can serve as endogenous danger signals that trigger the nucleotide-binding leucine-rich repeat-containing pyrin receptor 3 inflammasome and the subsequent production of IL-1β provides a direct linkage between cholesterol deposition and arterial inflammation.9 Moreover, recent Mendelian randomization studies suggest that genetic polymorphisms in the IL-6 receptor signaling pathway could be those most likely to have regression of atherosclerosis, event rates.10,11 With this hindsight, our decade-old observation that cholesterol lowers low-density lipoprotein-cholesterol and reduces inflammation seems less controversial.12 Multiple major clinical trials confirm that patients who achieve low levels of low-density lipoprotein-cholesterol, and whose greatest benefits of statin therapy accrue among those with low levels of both biomarkers.13 Furthermore, patients with lower CRP in response to statin therapy also seem to be those most likely to have regression of atherosclerosis, presumably a reflection of upstream changes in the inflammatory response that are detected by downstream CRP levels, even if CRP itself has no direct activity.14–16 Collaborative work by investigators worldwide presently underway could bring the issue of inflammation and vascular disease full circle. To address the inflammatory hypothesis of atherothrombosis directly, the clinical trials community has initiated 2 hard-outcomes studies using pathway approaches that reduce upstream proinflammatory cytokines (such as IL-1, tumor necrosis factor-α, and IL-6) as well as downstream biomarkers (such as CRP and fibrinogen). The first trial, the Canakinumab Anti-inflammatory Thrombosis Outcomes Trial (CANTOS), is almost fully enrolled and addresses whether a human monoclonal antibody with high specificity for IL-1β can reduce recurrent vascular events.17 The second trial, the National Heart, Lung, and Blood Institute–sponsored Cardiovascular Inflammation Reduction Trial (CIRT), has just begun enrollment and addresses whether low-dose methotrexate, a generic anti-inflammatory drug widely used to treat rheumatoid arthritis, can safely reduce recurrent vascular events.18 These 2 multinational trials, involving 17,000 patients, represent a major movement beyond the marker versus mediator debate and on to a translational endgame testing whether inflammation inhibition will or will not have a major role in cardiovascular clinical practice.

Disclosures

Dr Ridker is listed as a coinventor on patents held by the Brigham and Women’s Hospital (BWH) that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes mellitus that have been licensed to Siemens and AstraZeneca, and is the Principle Investigator of the Cardiovascular Inflammation Reduction Trial (funded by the National Heart, Lung, and Blood Institute) and of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (funded by Novartis). Neither Dr Ridker nor the BWH will receive any royalties related to the use of the C-reactive protein test in either of these trials.

References


Key Words: Editorials ■ atherothrombosis ■ C-reactive protein ■ clinical trials ■ inflammation ■ interleukin-1 ■ interleukin-6
Inflammation, C-Reactive Protein, and Cardiovascular Disease: Moving Past the Marker

Versus Mediator Debate

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