

The Story Behind the Acute-phase Reactants

To the Editor:

Physicians usually try to quantify complex biological phenomena through simple laboratory assays. So several tests have been developed to assess the inflammatory response, a nonspecific intricate system of response against different aggressors that includes multiple mechanisms of innate and adaptive immunity. These tests are often used interchangeably or redundantly, on the assumption that all evaluate the same processes. In this vein Crowson and colleagues¹ compared the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) to assess inflammation in patients with rheumatoid arthritis (RA). The authors conclude that it is not necessary to obtain both measures and that, where available, the CRP alone may be preferred for disease activity assessment. In the accompanying editorial², Dr. Wolfe critically discusses these conclusions and knocks down some myths about both laboratory tests; however, we are convinced that we must go one step beyond.

The term acute-phase reaction was coined long ago, and the core concept of this response has been evolving over time. Now it is clear that the acute-phase reaction is not a global, well coordinated response; rather, the various acute-phase reactants are independently regulated³. Since each acute-phase reactant is the result of a unique immune circuit, it is ingenuous to consider that it evaluates the inflammatory process as a whole. Indeed, while the ESR is a surrogate marker of the presence of various cationic proteins that promote the formation of *rouleaux* structures⁴, CRP is a protein massively induced as part of the innate immune response to tissue injury.

More importantly, clinicians should bear in mind that the proteins induced during an inflammatory response have intrinsic physiological effects beyond their clinical application as markers of inflammation. For instance, cumulative evidence suggests that the ultimate effect of CRP action might be antiinflammatory⁵. Besides its extended use as an acute-phase reactant, CRP has the physiological function to bind to damaged cell membranes and small ribonucleoproteins in apoptotic cells⁶. Membrane-bound CRP is recognized by C1q and activates the early components of the classical complement pathway; however, CRP also provides secondary binding sites for factor H, a complement regulatory protein that accelerates the decay of C3 and C5 convertases and destabilizes the amplification loops, thus attenuating the formation of the membrane-attack complexes⁷. Additionally, the engagement of the FcγR on macrophages by CRP has striking effects on the phagocytosis of apoptotic cells. Then, ingestion of apoptotic cells in the presence of early components of the classical complement pathway activation, but not assembly of the terminal complement components, results in inhibition of the production of proinflammatory cytokines (as tumor necrosis factor and interleukin 1β) through mechanisms involving overproduction of transforming growth factor-β (TGF-β), a prototypical antiinflammatory cytokine⁸.

The most dramatic expression of the importance of CRP as an anti-inflammatory molecule that prevents autoimmunity comes from systemic

lupus erythematosus. The underpowered CRP response seen in patients with lupus nephritis is very likely a contributory factor leading to impaired handling of apoptotic cells and clearance of immune complexes, enabling the development of immune response to self^{3,7}.

Briefly, we are certain that every acute-phase reaction can give us much more information than just a measure of inflammation. It must be clear that each biomarker may also have different roles in selected clinical conditions, and it is not appropriate to replace one with another. The time has come for rheumatologists to understand the story behind and the meaning of each acute-phase protein in specific clinical settings.

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