Cardiovascular biomarker questioned

A study in the *Journal of the American Medical Association* addresses a long-standing controversy in cardiovascular medicine: does a protein in the bloodstream associated with cardiovascular disease, C-reactive protein (CRP), actually cause disease? The analysis, an amalgamation of data from 120,000 individuals, suggests that the answer is no[1]. Paul Elliott *et al.*[1] found no increased risk for cardiovascular disease in people with gene variants that increased levels of CRP. We asked three experts how the findings changed their views.

> "CRP may have great clinical utility in guiding management of those in the important gray zone of risk—Peter Libby"

Alberto Mantovani:

The lack of conservation of CRP regulation and function between mouse and humans has prevented stringent genetic testing of its pathophysiological role in preclinical models, whereas such evidence is available for PTX3, a member of the same molecular family, pentraxins, and a candidate marker in coronary heart disease[2]. The new findings provide genetic evidence arguing against a functional role of CRP in the pathogenesis of coronary heart disease.

The strength of this study rests in its experimental design, which includes an unbiased identification of genetic loci associated with variation in CRP levels and mendelian randomization of over 28,000 affected individuals and 100,000 control individuals. A major intrinsic limitation is that even for the *CRP* locus, the effect of genetic variants on blood levels is not dramatic. Therefore, these results argue against, but do not formally disprove, the notion that CRP is a valuable therapeutic target in cardiovascular disease.

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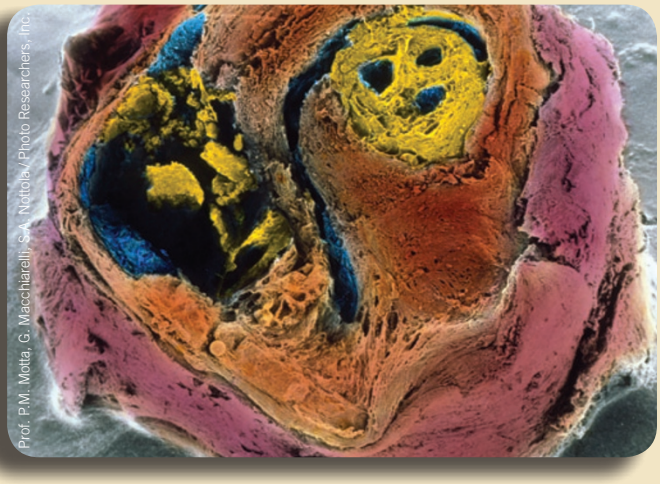

Atherosclerosis: does CRP cause this?

Mark Pepys:

The idea that CRP promotes atherosclerosis arose from inappropriate conflation of association and causality. The association between marginally raised baseline CRP values and cardiovascular disease risk in general populations is rather modest and results from the fact that the known causative risk factors, such as obesity, diabetes, high blood pressure, smoking and poor socioeconomic status, all increase CRP production.

The rigorous, large-scale study of Elliott *et al.*[1] strengthens existing, robust clinical and experimental evidence that CRP does not promote atherosclerosis or cause heart attacks. In contrast, there is compelling clinical and experimental evidence that high, acute-phase concentrations of CRP exacerbate tissue damage when acute myocardial infarction has occurred and that CRP may be a valid therapeutic target in this condition.

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COMPETING INTERESTS STATEMENT

The author declares competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturemedicine/.

Peter Libby:

One must not confound CRP's established role as a risk marker with its possible involvement in the causal pathway for complications of atherosclerosis. Recent mendelian randomization studies, including that of Elliott *et al.*[1], have shown that polymorphisms in the *CRP* gene associated with higher CRP levels are not associated with increased cardiovascular risk, arguing against CRP's role as a mediator of events.

As markers of risk, traditional algorithms that do not include such a marker of inflammation do quite well in those with high or low risk. Yet CRP, measured with a highly sensitive assay (hsCRP), can correctly add information about risk in the intermediate risk group, a smaller sector, but one in which many events occur. If you spread out the predictive ability of hsCRP as an independent risk marker across a whole population, its added value over traditional indicators might seem modest by some statistical measures, but hsCRP may have great clinical utility in guiding management of those in the important gray zone of risk.

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1. Elliott, P. *et al.* Genetic loci associated with C-reactive protein levels and risk of coronary heart disease. *J. Am. Med. Assoc.* **302**, 37–48 (2009).
2. Salio, M. *et al.* Cardioprotective function of the long pentraxin PTX3 in acute myocardial infarction. C*irculation* **117**,1055–1064 (2008).