C-reactive protein and its role in the pathogenesis of myocardial infarction

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C-reactive protein (CRP), the classical acute phase reactant, has for some time contributed to both the diagnosis and management of a wide range of infective and inflammatory conditions. More recently with the advent of high sensitivity assays, the hypothesis that atherosclerosis is an inflammatory disease has been strengthened. "Elevated" CRP values predict a poor outcome for patients suffering from unstable coronary syndromes as well myocardial infarction, and large epidemiological surveys have shown that baseline values of CRP can predict future cardiovascular events in those at risk, as well as those otherwise well. Increasingly a direct role for CRP in the pathogenesis of atherosclerosis and post-myocardial infarction inflammation has also been suggested, and CRP itself may prove to be a future therapeutic target in the treatment of atherosclerosis and its consequences.

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Inflammation is now recognised as a major feature of atherosclerosis[1] and there is significant evidence for an association between systemic inflammation, and the occurrence of stroke, peripheral arterial disease, unstable angina and myocardial infarction[2-4]. C-reactive protein (CRP), the classical acute phase protein, is an exquisitely sensitive systemic marker of inflammation and tissue damage[5], which has been shown to be predictive, even within the range previously considered to be normal, for future atherothrombotic events[4,6-11]. Not surprisingly, CRP values correlate closely with other diverse markers of inflammation, some of which also have a predictive value, albeit generally less significant[12,13]. However, certain properties of CRP itself make it particularly interesting; not only does it bind selectively to low density lipoprotein (LDL)[14] (especially oxidised and modified LDL as found in atheromatous plaques[15]), but it is also found deposited in the majority of such plaques[16,17] and it has a range of pro-inflammatory properties that could potentially contribute to the pathogenesis, progression and complications of atherosclerosis[18-20]. With regard to myocardial infarction in particular, there is a predictable CRP response to myocardial necrosis[21,22], and the peak values post-myocardial infarction predict outcome[23,24]. Moreover, CRP is deposited within all acute myocardial infarcts[25,26], and there is compelling *in vivo* evidence that CRP contributes, in a complement dependent manner, to the severity of post-infarction inflammation[27]. Of note there is also substantial evidence between antecedent or concurrent systemic inflammatory activity and the occurrence of myocardial infarction[28].

For the purpose of this minisymposium we will focus on the possible role of CRP, as well as general inflammation, in the events surrounding myocardial infarction. Although there has been a torrent of reports on the predictive value of CRP with respect to atherothrombotic events, the stimuli that trigger the very low grade up-regulation of CRP production that predicts coronary events in general populations[4,9,10], or the more substantial CRP values associated with poor prognosis in severe unstable angina[7,29,30] or after angioplasty[31], have not been clearly identified. A number of factors have been associated with CRP values, in particular higher values are strongly associated with increased body mass index[32] as well as with many other features of the insulin resistance or metabolic syndrome[33], including frank diabetes mellitus[34]. In view of the contribution of adipocytes to resting interleukin-6 levels this association is not surprising[35]. However it also suggests that some or even most of the inflammatory marker profile associated with increased atherothrombotic risk in the population at large, may not be triggered by inflammation or tissue

damage in the classical sense. Rather it may be a sign of a particular metabolic state which happens also to be pro-atherogenic, or at least predisposing to atherothrombotic events. A further intriguing association exists between endothelial dysfunction, a marker of atherosclerosis-related coronary events, and systemic inflammation[36,37].

As alluded to earlier on, there is the possibility that CRP itself may have a significant pathophysiological role in atherogenesis, plaque destabilisation and atherothrombosis. The binding of CRP to lipids, especially lecithin, and to plasma lipoproteins, especially what was formerly called β-lipoprotein, has been known for over 60 years, and we first suggested a possible relationship to atherosclerosis when we showed that aggregated, but not native, non-aggregated, CRP selectively bound LDL from whole serum[14,38]. We looked hard for CRP in various arterial lesions but failed to detect it convincingly by immunofluorescence techniques[39]. However, recent studies with more sensitive immunoperoxidase methods[16] and with appropriately rigorous controls for specificity of CRP staining[17] have convincingly shown that CRP is indeed present in most plaques, and we have confirmed this in our own laboratory.

The presence of CRP within the plaque and its binding to LDL may have a number of effects. First, the capacity of aggregated and ligand-complexed human CRP to activate the classical complement pathway has long been known[40,41]. Ligand bound CRP thus has the ability to unleash the major opsonic and chemotactic functions of the complement system. Second, bound CRP *may* (and there is conflicting evidence in the literature[42]) be recognised by a subset of cellular Fc(γ) receptors and so possibly directly activate phagocytic cells[43-45]. Third, CRP has been reported to stimulate tissue factor production by peripheral blood monocytes and could thereby have important pro-coagulant effects[46,47]. However the latter actions of CRP have not been well defined or robustly controlled for; all the published work has been done with commercially sourced CRP of incompletely defined provenance/purity, and there have been few robust specificity controls. Nevertheless if the phenomenon is reproducible it provides a possible direct link between increased CRP production and atherothrombotic events.

The development of drugs to block CRP binding *in vivo* is now a high priority for us[48]. In addition to affording potential cardioprotective therapy in acute myocardial infarction, such drugs will provide the means to investigate whether CRP contributes to pathogenesis of atheroma and/or atherothrombosis. We believe that development of new reagents with specific anti-inflammatory or anti-CRP properties will, reasonably soon, not only represent a new therapeutic option, but also help to answer some of the exciting, but unsolved, questions, about inflammation and CRP.

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