C-reactive protein and atherosclerosis: *Quo Vadis?*

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In recent years numerous studies have demonstrated a direct association between elevated levels of C-reactive protein (CRP) and future risk of cardiovascular disease. An intriguing question is whether CRP represents just a sensitive marker of systemic inflammation, a process known to play an important role in atherothrombogenesis, or whether it may contribute actively to atherosclerotic lesion formation.

In this paper we summarize the current evidence for an involvement of CRP in atherogenesis and we speculate about potential therapeutic implications these observations might have.

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The role of elevated C-reactive protein (CRP) as a risk marker for cardiovascular diseases, including coronary heart disease[1], stroke[2] and peripheral arterial disease[3] is well established through consistent results from a number of prospective studies. But CRP also conveys important prognostic information in the setting of the acute coronary syndrome. Subjects presenting with unstable angina or non-ST-segment elevation myocardial infarction and increased levels of CRP are candidates for a variety of adverse events like recurrent angina, ST-segment elevation myocardial infarction, or coronary death. This holds true short term for in-hospital complications but also long term over years as recently convincingly shown by data from the FRISC trial[4]. Even in the presence of the results of troponin measurements, CRP adds relevant prognostic information[5]. Moreover, persistent elevation of CRP levels after optimal treatment of unstable angina according to current strategies, measured at the time of hospital discharge, are predictive of recurrent events[6]. Thus, from the clinical point of view, CRP testing represents a valuable additional diagnostic tool. Interestingly, subjects with unheralded acute myocardial infarction showed normal CRP levels in the majority of cases, compared to subjects with pre-infarction angina pectoris[7]. This may serve as a clue that different pathophysiology is involved in subjects with an acute coronary syndrome.

In contrast to the consistent clinical evidence for a role of an inflammatory response in atherosclerotic disease, our knowledge of the underlying causes of such low-grade inflammation is scarce. Although experimental data clearly document the presence of inflammatory cells like monocyte-derived macrophages, T-cells and mast cells in the plaque, in particular in the area prone to rupture, the primary cause for their accumulation and activation in the subintimal space remains largely unclear[8]. These cells have been found to express a number of proinflammatory cytokines and other mediators which play an important role in plaque progression and finally contribute to plaque destabilization and rupture. In the light of such lack of our pathophysiological understanding, several recent findings on CRP are of particular interest. These findings relate to the question whether CRP might contribute actively to the pathogenesis of atherosclerosis[9-12]. When it was demonstrated in the past that CRP interacts with apolipoprotein B-containing lipids in humans[13], this issue already became a matter of debate[14]. Due to methodological problems, CRP could not be detected in atherosclerotic tissue at this time[15], and thus the matter disappeared from international discussions. Few reports on the ubiquitous CRP deposition in human atherosclerotic lesions were hardly reproducible[16,17]. More sensitive immunoperoxidase techniques performed in our laboratory, however, have recently shown that CRP indeed is present in human atherosclerotic lesions[9,11], and this

has been confirmed by other laboratories[10]. The molecule is detectable in the arterial intima in the earliest stages of atherogenesis and accumulates with lesion progression.

This latter finding has possibly provided new insights into the pathogenesis of atherosclerosis, because CRP displays a number of proinflammatory properties that may explain phenomena in atherogenesis which are not yet understood:

• ligand bound CRP is known to activate the complement system[18]. Complement activation has long been observed to be an important pathogenic feature both in human and in experimental atherogenesis[19,20], but the molecular mechanisms underlying complement activation remained largely unclear. Co-localization of CRP and the terminal complement complex C5b-9 in early atherosclerotic lesions suggests CRP as a major complement activating molecule in the arterial wall[9], even though there is a discussion about the efficiency of CRP-mediated complement activation in generating C5b-9[21];

• CRP activates monocytes/macrophages[11,22] and inhibits neutrophils[23]. Thus, in addition to other chemoattractants, e.g. monocyte chemotactic protein-1 (MCP-1), CRP may act as a chemoattractant for monocytes/macrophages *in vivo* and may thereby be intimately involved in one of the major cellular events in the formation of atherosclerotic lesions, namely monocyte infiltration. The inhibition of neutrophil chemotaxis and binding of neutrophils to endothelial cells may well explain why hardly any neutrophils are found in the lesion although potent neutrophil chemoattractants, e.g. C5a, must be generated within the arterial wall;

• CRP displays calcium dependent *in vitro* binding to low-density lipoprotein (LDL)[13] and thus, may enter the arterial wall bound to lipids or may be entrapped in the intima by deposited lipids. The observation that CRP co-localizes with foam cells in atherosclerotic lesions[9] together with the fact that CRP complement dependently opsonizes biological particles[24] led to the investigation of CRP-mediated uptake of native LDL by macrophages. This mechanism may contribute significantly to foam cell formation in the atherosclerotic lesion[12]. Such observation may be of particular interest as, in contrast to the major former hypotheses on foam cell formation in atherogenesis, these data suggest a mechanism for LDL uptake by macrophages without any need for biochemical modification of LDL. Both, CRP-induced monocyte chemotaxis and CRP-induced LDL uptake by macrophages are mediated via specific CRP receptors which have recently been identified as the immunoglobulin receptor FCγRIIa[25].

Taken together, these recent findings on the pathophysiological role of CRP in atherogenesis may have several implications for future research including the implementation of therapeutic strategies in cardiovascular diseases:

• CRP plasma levels may become a target for intervention. Although thus far no drug for specifically lowering of CRP is available there is indirect evidence from trials with statins[26,27], ACE-inhibitors[28], and aspirin[29] that the net clinical benefit of these compounds may, at least in part, be explained by their anti-inflammatory properties;

• it is intriguing to speculate that direct interference with CRP-mediated effects either on the receptor level or on the level of CRP-mediated complement activation[9,30] may influence progression of atherosclerosis and its complications.

In summary, the recent research on CRP, being an ancient compound of innate immunity, has provided new insights in a possibly important link between the immune system and the lipid metabolism in humans. This might be of major importance for the advancement of our understanding of atherosclerosis and may open new horizons to combat this far spread disease.

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