C-reactive protein (CRP) is a powerful cardiovascular risk marker. Evidence suggests that this may be due to its direct proatherogenic properties. Because of different biological functions of CRP in different species, an appropriate animal model for the study of its role in atherogenesis is difficult to set up. Binding to low density lipoprotein (LDL), activation of the complement system and interaction with monocyte/macrophages are rigorously defined pathogenic properties of CRP which might contribute to an active role of the molecule in human atherogenesis. Furthermore, direct effects on arterial wall cells, i.e. endothelial cells and smooth muscle cells, have been reported. The molecular basis of CRP interaction with these cells, however, remains unclear. Should CRP indeed be actively involved in human atherogenesis, the molecule may become a target for therapy. Pharmaceutical companies develop CRP-inhibitors.

Key words: C-reactive protein, complement, atherosclerosis

Introduction

C-reactive protein (CRP) is the prototype acute phase protein in humans and plays an important role in innate immunity (Mortensen, 2001; Volanakis, 2001). In acute phase response, plasma CRP concentrations may rise up to 1000-fold compared to normal. CRP possesses diverse biological functions like opsonizing pathogens (Kindmark, 1971; Volanakis and Kaplan, 1971; Mortensen et al., 1976; Kindmark, 1971; Mold, 2001) or damaged cells (Martin et al., 1995; Gershov et al., 2000) and regulating inflammatory processes (Mold et al., 2002). One of the major and most rigorously defined biological functions of CRP in humans is activation of the complement system via the classical pathway (Kaplan and Volanakis, 1974; Volanakis and Kaplan, 1974; Claus et al., 1977; Volanakis, 1982).

CRP - a cardiovascular risk marker

CRP was established as a sensitive marker of inflammation a long time ago (Tillett and Francis, 1930). Accumulating evidence from various epidemiological prospective studies over the recent years indicates that CRP is an important marker of future cardiovascular risk (Danesh et al., 1998; 2000; Koenig et al., 1999; Speidel et al., 2002; Haidari et al., 2001; Folsom et al., 2002). If subjects are both in the top quintile of CRP and low density lipoprotein (LDL) cholesterol plasma levels their risk of a first cardiovascular event is increased up to eight- to nine-fold (Rifai and Ridker, 2001). Recently, data from a large population study (Women´s Health Study) demonstrated worse survival rates for women belonging to the upper quintile of CRP plasma levels as compared to those from the upper quintile of LDL cholesterol plasma levels (Ridker et al., 2002). These data suggest that CRP plasma levels are a stronger predictor of cardiovascular events than LDL cholesterol plasma levels. The question arises whether CRP is just a cardiovascular risk marker or whether it is a cardiovascular risk factor intimately involved in the pathogenesis of atherosclerosis.

CRP - a cardiovascular risk factor?

Data from a variety of experimental studies indicate an active role of CRP in atherogenesis. However, some of these studies are seemingly preliminary and the described effects need to be investigated in detail before the impact of such studies can be assessed properly. Furthermore, it is not yet proven in an animal model that CRP is causal in atherogenesis. It is difficult to set up an appropriate animal model as the biological functions of CRP differ from species to species.

The following paragraph summarizes the evidence for an involvement of CRP in atherogenesis and comments on the plausibility of results.

1. CRP deposition in human atherosclerotic lesions
C-reactive protein and atherosclerosis

Mechanisms of CRP action in atherosclerosis

CRP activates the complement system

Ligand-bound CRP activates the complement system via the classical pathway (Kaplan and Volanakis, 1974; Volanakis and Kaplan, 1974; Claus et al., 1977; Volanakis, 1982). It has been known for many years now that complement plays a role in atherosclerosis (Torzewski et al., 1997a,b). Animals lacking components of the complement system are protected against diet-induced atherogenesis (Geertinger and Soerensen, 1977; Schmiedt et al., 1998; Buono et al., 2002). Various complement proteins, including the terminal complement complex C5b-9, have been shown to deposit in human and animal atherosclerotic lesions (Niculescu et al., 1985; Vlaicu et al., 1985; Seifert et al., 1989; Torzewski et al., 1997a,b), but not in healthy arterial tissue. Potential complement-activating molecules have been detected in atherosclerotic lesions in recent years (Seifert et al., 1989, 1990). Given the role of CRP as a robust cardiovascular risk marker and given the fact that CRP colocalizes with activated complement fragments in atherosclerotic lesions (Torzewski et al., 1998; Yasojima et al., 2001), CRP-mediated complement activation in the arterial wall may be considered as an important pathogenic feature in human atherogenesis. It is tempting to speculate that CRP, bound to LDL or modified LDL in the arterial wall, might play a pivotal role in atherogenesis by local perpetuation of the humoral immune response via activation of the complement system.

CRP interacts with phospholipids on cell membranes

CRP-binding to cells has long been investigated. It was initially demonstrated that CRP binds to necrotic cells or damaged cell membranes only (Kushner and Kaplan, 1961), but not to normal cells. CRP was shown to bind to phosphorylcholine in the membranes of damaged cells and this process requires partial hydrolysis of the membrane phospholipids (Volanakis and Wirtz, 1979). Also, CRP was reported to bind to apoptotic cells (Gershov et al., 2000). In the light of the aforementioned reports of CRP-mediated activation of
vascular cells (cells that are not known to express CRP-receptors), it has to be considered that CRP-induced effects in these cells are not mediated via specific receptors but may be due to an interaction of CRP with phospholipids of damaged cells in cell culture.

**CRP interacts with cellular CRP receptors**

CRP-binding to cellular receptors has long been investigated. CRP-Rs were demonstrated to be present on various types of leukocytes: polymorphonuclear neutrophils (PMNs) (Müller and Fehr, 1986; Buchta et al., 1987); blood monocytes (Zeller et al., 1986); and lymphocytes (Mortensen et al., 1975; James et al., 1981). Whereas some reports provided evidence for specific CRP-receptors on leukocytes (Tebo and Mortensen, 1990; Zen et al., 1997) other experiments demonstrated interaction with Fc-receptors (Marnell et al., 1995; Bharadwaj et al., 1999). The high affinity IgG-receptor FcγRI was identified as a low affinity CRP-receptor (Marnell et al., 1995), whereas, recently, the low affinity IgG-receptor FcγRIIA was described as the major receptor for CRP (Bharadwaj et al., 1999). There are two codominantly expressed allelic variants of FcγRIIA resulting in a change at amino acid position 131 displaying different affinity to IgG1 and IgG2. FcγRIIA-131R/R has been defined as the “high responder” form of the receptor and FcγRIIA-131H/H as the “low responder” form for IgG binding. It has been reported that these two allelic variants confer distinct CRP-binding to leukocytes (Stein et al., 2000). In monocytes, CRP-binding to cells expressing FcγRIIA-131H/H was hardly detectable whereas significant binding has been demonstrated for FcγRIIA-131R/H and FcγRIIA-α-131R/R. However, as the initial reports (Bharadwaj et al., 1999; Stein et al., 2000) used anti-CRP antibodies in order to demonstrate CRP-binding to FcγRIIA it was suggested that detection of CRP-binding to FcγRIIA results from interaction of the Fc-part of the anti-CRP antibodies with FcγRIIA itself (Saeland et al., 2001). In experiments using F(ab’)2 fragments of anti-CRP antibodies (Clone CRP 8, Sigma), no CRP-binding to FcγRIIA-R131 was found on polymorphonuclear leukocytes and FcγRIIA-transfected IIA.6 cells. Other authors proposed that the observation of CRP-binding to FcγRIIA might be due to IgG-contamination of the CRP reagent used in the binding studies (Hundt et al., 2001). Finally, Ca-dependent high affinity CRP binding to the extracellular portion of FcγRI has recently been demonstrated using surface plasmon resonance (BIACore® system) (Bodman-Smith et al., 2002). This observation again contradicts previous results of low affinity CRP-binding to FcγRI expressed on COS-7 cells (Marnell et al., 1995).

Thus, the data surrounding the area of CRP binding to cellular receptors are confusing and the question of the major cellular CRP-receptor has not yet been resolved. In the light of increasing evidence for an involvement of CRP in the pathogenesis of atherosclerosis the identification of the major CRP receptor and its consecutive blockage might be of therapeutic relevance.

In summary, a causal role for CRP in atherogenesis is most likely but not yet proven. CRP may be a target for therapy. Potential therapeutic strategies involve lowering CRP plasma levels by direct inhibition of CRP synthesis in hepatocytes, interfering with CRP-mediated complement activation or blockage of cellular CRP-receptors. Pharmaceutical companies develop CRP-inhibitors.

**References**


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Accepted April 17, 2003