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Review

CRP, a major culprit in complement-mediated tissue damage in acute myocardial infarction?

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1. Introduction

Acute myocardial infarction (AMI) is one of the major causes of mortality and morbidity in the western world. About 1.5 million individuals in the United States suffer an acute myocardial infarction annually, of which approximately 500,000 are hospitalized. Mortality is due to arrhythmia, cardiac rupture and acute heart failure, whereas morbidity often results from chronic heart failure. Classic acute myocardial infarction with extensive necrosis occurs when perfusion of myocardium is reduced severely below its needs for an extended interval (hours), causing profound, prolonged ischemia resulting in permanent loss of function through cell death by coagulation necrosis. In contrast, if restoration of myocardial blood flow follows after a short period of flow deprivation, loss of cell viability generally is limited. Reperfusion of ischemic myocardium therefore is necessary to salvage tissue from eventual death. Paradoxically, reperfusion after intermediate periods of ischemia is associated with pathologic changes that result in further expansion of the initiated tissue damage. In ischemia/reperfusion experiments in rabbits, Farb et al., for example, showed that a subset of myocytes in border areas of the ischemic region, viable at the beginning of reperfusion, subsequently progress to irreversible injury during reperfusion [1]. Cell death during reperfusion does not occur primarily via necrosis, but also results from apoptosis, via upregulation of caspase activity [2]. This 'reperfusion injury' of the myocardium shares many charac-

Abbreviations: AMI, Acute myocardial infarction; C1-INH, C1 esterase inhibitor; CoVF, Cobra venom factor; CRP, C-reactive protein; CR1, Complement receptor 1; ICAM-1, Inter cellular adhesion molecule-1; MAC, Membrane attack complex; MBL, Mannose binding lectin; PLA_2, Phospholipase A_2 ($sPLA_2$—Secretory phospholipase A_2, $cPLA_2$—Cytosolic phospholipase A_2); PMN, Polymorphonuclear granulocytes; PTCA, Percutane transluminal coronary angioplasty; RCA, Regulator of complement activation; rt-PA, recombinant tissue-type plasminogen activator; SK, Streptokinase; UAP, Unstable angina pectoris

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teristics with an inflammatory response. For example, reinstitution of the coronary circulation in an area in which myocardial cell injury has already occurred, markedly augments the influx of leucocytes [3–5]. However, not only following reperfusion, but also under conditions of permanently impaired blood flow, an inflammatory response ensues in the ischemic myocardium, which can contribute to the final infarction size. For example, inhibition of this inflammatory response by means of corticosteroids, given as late as 6 h after coronary occlusion, reduces infarction size by about 35% compared with untreated control animals [6]. Consequently, during myocardial ischemia, complicated interactions occur between ischemic cardiomyocytes, inflammatory cells (like neutrophils), cytokines, complement factors and acute phase proteins [7,8]. Although these interactions in permanent ischemic conditions may differ from those ensuing in reperfused ischemic myocardium, in both situations they may enhance myocardial damage.

2. Acute myocardial infarction and the complement system

As part of the inflammatory response in ischemic myocardium, complement activation was first demonstrated by Hill and Ward in the early 1970s. They showed that complement activation products generated in the infarcted myocardium were responsible for the infiltration of neutrophils [9]. The complement system consists of a number of plasma proteins (as well as a number of membrane bound proteins) that comprise approximately 20% of the plasma globulin fraction. The system belongs to the plasma cascade systems, and can be activated via the classical, alternative or lectin pathway [10]. Complement proteins and fragments derived therefrom are involved in many aspects of the inflammatory response. They mediate chemotaxis and opsonisation of particles or microorganisms, stimulate the release of enzymes from leukocytes, induce vasodilatation, enhance vascular permeability and influence the cytokine network and the coagulation system [11–13]. Recent research also indicates a possible role of the complement system in the induction of apoptosis [14]. Thus, in addition to its role as a defense mechanism, the complement system is regarded as an important mediator of inflammation and subsequent cell death.

Local activation of the classical pathway of complement in infarcted myocardium—as reflected by deposition of activated fragments of this pathway—has been observed in various animal models for AMI [8,15,16]. Notably, this activation occurs in ischemia with or without reperfusion. In an animal model for ischemic cardiac damage, consisting of 50 min of ischemia followed by 3 h of reperfusion, the alternative complement pathway has also been implicated to play a role in mediating tissue damage [17]. In a rat model, in which 60 min of ischemia were followed by 30 min of reperfusion, the ischemic area at risk was found to contain deposits of mannose binding lectin (MBL) and complement fragment C3, which was not observed in non-reperfused hearts. These findings imply that the lectin pathway may also contribute to activation of the complement system in AMI, particularly after reperfusion [18]. Not only deposition of more upstream activating products such as C1q, MBL, C4 and C3 has been shown to occur in ischemic myocardium, but also that of the downstream C5b-9 membrane attack complex (MAC). Experimental studies in rabbits show the presence of this macromolecular complex on cardiomyocytes and endothelial cells in ischemic areas [19]. It should be noted that in these experiments, myocardial ischemia without reperfusion resulted in a late deposition of C5b-9 in the infarcted areas, in contrast with the rapid appearance of C5b-9 upon reperfusion of the ischemic myocardium (as soon as 30 min after onset of reperfusion).

In human post mortem studies, deposition of activated fragments of the classical pathway and C3 has also been demonstrated in ischemic myocardium of patients who died subsequent to AMI [20,21]. These depositions were present in patients with an estimated infarct duration of more than 12 h up to 14 days. In patients with an estimated duration of 0–12 h, complement depositions were not observed, except for one patient who had been treated twice with reperfusion therapy. The presence of the downstream product C5b-9 has also been shown in ischemic areas of the heart of patients that died subsequent to AMI [22].

In addition to deposition of complement proteins in the ischemic myocardium, circulating levels of activated complement proteins and fragments therefrom have also been shown to increase in plasma following AMI both in animal models as well as in patients. For example, in ischemia/reperfusion experiments in pigs, the levels of the anaphylatoxins C3a and C5a significantly increase after 60 min of coronary occlusion and subsequent reperfusion [23]. In agreement with these study results in animals, patients with AMI have elevated plasma levels of activation products, whereas in patients with angina pectoris (AP), this was not observed [24]. In patients with AMI treated with thrombolytic therapy, levels of the anaphylatoxin C4a also increase [25]. In recent studies, our group showed a biphasic elevation of the complement fragments C3a, C3b/c and C4b/c in patients suffering from AMI: the first peak being present at an infarct duration of 0–12 h and a second at 12–48 h and later on (manuscript submitted, see Fig. 1). This first phase of activation was particularly prominent in the patients receiving thrombolytic agents, as has been found by others as well [26].

Though these human and animal studies show the deposition of complement fragments in ischemic areas and the elevation of complement activation products in plasma, the origin of the fragments deposited in the ischemic tissue is the subject of ongoing studies. It is generally assumed that the liver is the primary source for the production of complement proteins. However, Yasojima et al. demonstrated that ischemia in a solitary rabbit heart in Langendorf setting, in particular when followed by reperfusion, provoked the rapid upregulation of mRNA encoding the complement proteins C3 and C9 [27]. A significant elevation of these mRNA was also shown in infarcted areas in a human post-mortem study [28]. Hence, activated complement fragments involved in

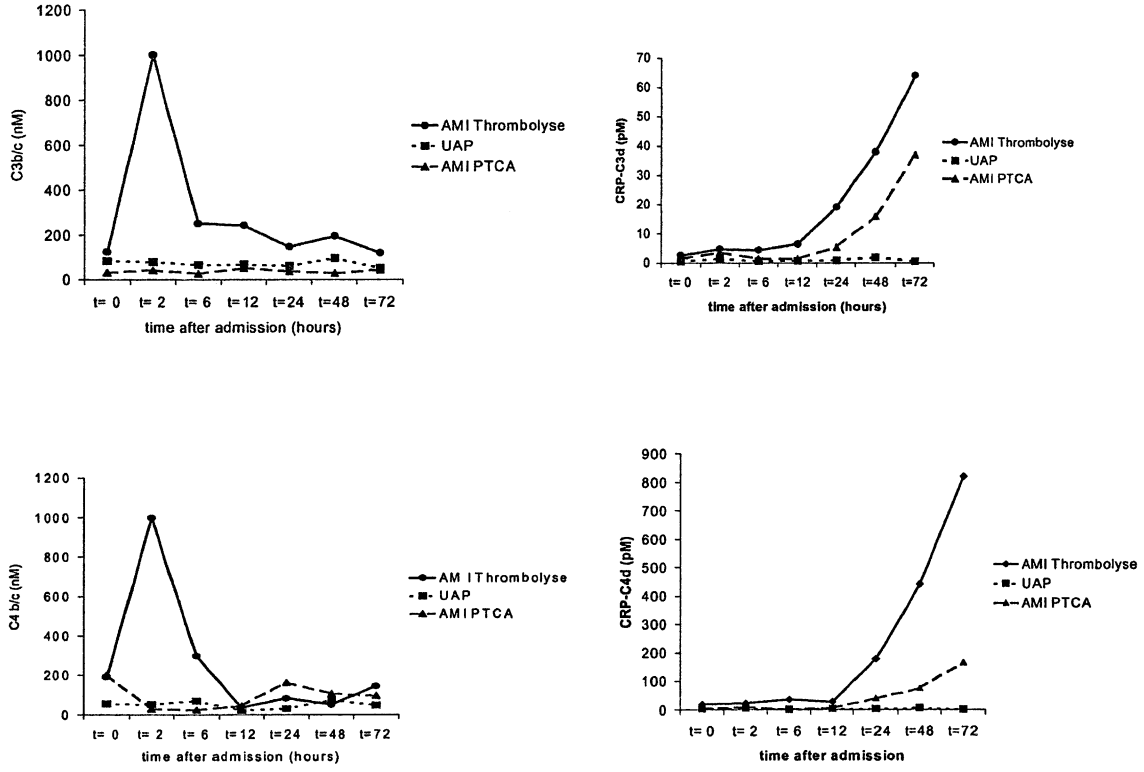

Fig. 1. CRP-complement complexes and activated complement (C4b/c and C3b/c) in plasma of three representative patients, one suffering from unstable angina pectoris (UAP), two suffering from acute myocardial infarction (AMI) and treated with either thrombolysis or percutane transluminal coronary angioplasty (PTCA). Patients arrived in the hospital within 4 h after the onset of first symptoms. Note the elevation of the activation products, C3b/c and C4b/c, in the episode of 0–12 h in the patient treated with thrombolysis.

the inflammatory response ensuing in the ischemia myocardium may not only originate from the circulation but may also be produced by ischemic cardiomyocytes.

3. Mechanisms of complement mediated damage in ischemic myocardium

A detrimental role for complement is suggested by the presence of MAC complexes on damaged muscle fibres in ischemic myocardial areas [29–31]. More conclusive evidence for such a role was obtained in rabbits deficient of complement factor C6, which cannot assemble a fully active MAC. These animals have a reduced infarct size in cardiac ischemia/reperfusion models as compared with C6-sufficient rabbits [32]. MAC may mediate effects via various mechanisms: the pore-forming ability of the MAC on the cell membrane can cause direct cell lysis [33–35]. MAC inserted in the cell membrane facilitates the movement of electrolytes across the cell membrane, resulting in a rapid increase in the intracellular Ca^{2+} concentration, which enhances the rate of cell death [36]. Sudden influx of calcium may be harmful to the cell in other ways as well, for example, by activation of calcium dependent phospholipases, increase of ATPase activity, and the uncoupling of oxidative phosphorylation in mitochondria [37,38]. Recent studies in experimental glomerulonephritis incriminate the MAC complex also as a factor inducing apoptosis [14,39]. To what extent the MAC contributes to apoptosis in ischemic myocardium remains to be determined. In addition to these direct cytotoxic effects, MAC at sublytic concentration may also have a number of other effect on target cells, such as induction of cytokines, changes in prostaglandin production, and others [40].

Complement activation can also facilitate activation of the coagulation cascade. For example MAC insertion in cell membranes is accompanied by the formation of membrane vesicles on the cell surface. These vesicles express binding sites for factor Va and support prothrombinase activity [41]. Complement activation with subsequent MAC formation can also result in the upregulation of tissue factor activity [42]. All of these effects promote coagulation and are, therefore, potentially harmful in AMI.

Animal studies indicate an important role of polymorphonuclear granulocytes (PMN), in particular because of their potency to generate oxygen radicals and enzymes, which can induce tissue damage in myocardial infarction [43,44]. Inter cellular adhesion molecule-1 (ICAM-1) effectively promotes the adherence of activated leukocytes, including PMN. Complement, in particular the anaphylatoxin C5a, is able to upregulate ICAM-1 by endothelial cells [45–47]. ICAM-1 expression in ischemic myocardium is upregulated during reperfusion [48–50]. We have found in post mortem studies in humans dying from AMI an increased ICAM-1 expression by non-viable cardiomyocytes in areas containing deposits of complement factors [21]. Moreover, the presence of CD66B on cardiomyocytes strongly suggested degranulation of PMN in these ICAM-1 positive areas, which was not observed in ICAM-1 negative areas. Notably, inhibition of ICAM-1 upregulation on myocytes significantly reduced neutrophil activity in jeopardized myocardium and afforded cardio protection in ischemia/reperfusion experiments [51]. Hence, ICAM-1 upregulation by cardiomyocytes may be an important event in the processes ultimately leading to death of these cells. Although the precise trigger for ICAM-1 expression by ischemic cardiomyocytes is not known, the time sequence between complement deposition and the expression of ICAM (see Fig. 2), as well as the observation that ICAM-1 expression is strictly restricted to complement-positive areas, suggests a role for complement. Complement and its activation products, in particular C5a, have the ability to provoke stimulation, aggregation and degranulation of PMN. Thus, complement activation may be responsible for the progressive leukocyte capillary plugging during myocardial ischemia, which may impair full restoration of the capillary flow upon reperfusion, the so-called “no-reflow” phenomenon [52].

Finally, complement activation products may have other effects on the myocardium as well. For example, administration of the anaphylatoxin C3a to guinea pigs causes tachycardia, impairment of atrioventricular conduction with subsequent arrhythmia, left ventricular contractile failure and coronary vasoconstriction, thus mimicking a number of cardiac changes occurring during AMI [53]. Similar cardiac changes were observed in rabbit ischemia/reperfu-

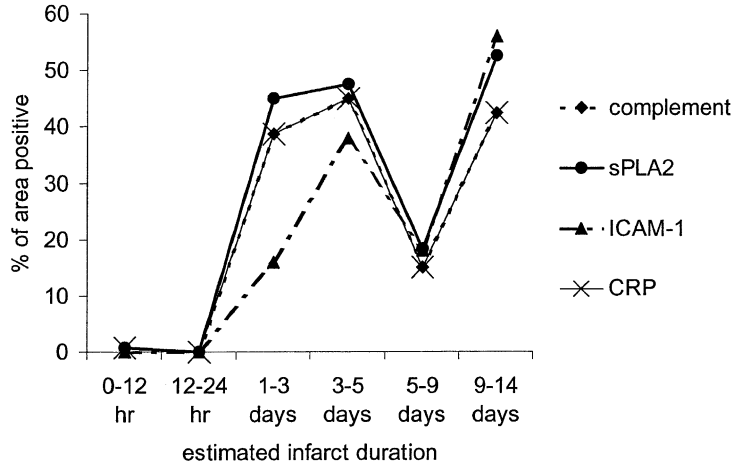

Fig. 2. Time frame of depositions of complement, CRP and $sPLA_2$ and the expression of ICAM-1 in human myocardial infarction, as derived from studies in patients dying within 14 days after onset of the disease. Tissue samples from the infarcted sites were analysed for the presence of CRP, complement (C4d), $sPLA_2$, and ICAM-1 by immunohistochemistry. The percentage of positive cardiomyocytes for the infarcted area is given. At the *X*-axis, the duration of the infarction is given. Note that the lines for CRP and complement coincide. Furthermore, all patients dying from infarctions of 9–14 days duration had suffered from re-infarction. So, presumably the increased depositions in infarctions of this duration are not representative for the normal course.

sion experiments although they were not attributed to the anaphylatoxins but to the MAC [54].

Thus, all of these studies together indicate a pivotal role for complement during AMI, not only by triggering cell death (directly or indirectly via PMN) but also by mediating hemodynamic alterations and myocardial dysfunction.

4. Inhibition of complement in AMI

Corticosteroids such as prednisone or dexamethasone are potent inhibitors of the inflammatory response. As early as 1953, Johnson et al. reported cortisone to have a profound effect on limiting myocardial damage during myocardial infarction in dogs [55]. Other animal studies confirmed these results [6,56]. Several clinical trials with positive as well as inconclusive results followed [57,58]. Corticosteroids, however, presumably because of their effects on cytokine and growth factor production, impair wound healing. Indeed, a higher incidence of left ventricular rupture in patients receiving high dose corticosteroid therapy was reported in some clinical trials [59,60]. Because of these negative effects on wound healing and scar tissue formation [61], corticosteroids were abandoned for the treatment of AMI.

As an alternative to corticosteroids, inhibition of complement has been explored in animal models as a therapy to reduce infarction size. Administration of cobra venom factor (CoVF) in vivo rapidly produces profound and sustained depletion of C3 and C5 [62,63]. For a long time, CoVF was the only agent available to manipulate complement in animals; most studies in experimental AMI have used CoVF as an inhibitor of complement. Cardioprotective effects of CoVF, resulting in reduced myocardial tissue damage, were demonstrated in animal ischemia/reperfusion experiments [64–66]. These cardioprotective effects were accompanied by reduced deposition of complement factors, except for C4, in the ischemic myocardium [64]. Positive hemodynamic effects of CoVF, like an increase of blood flow in the jeopardized area, with subsequent increase in oxygen utilization, have also been demonstrated [67].

Complement receptor 1 (CR1/CD35) is a member of the regulator of complement activation (RCA) protein super family. It is the only molecule of this family possessing decay-accelerating activity for both C3- and C5-convertases as well as factor I co-factor activity for the degradation of C3b and C4b [68]. Therefore, among the RCA family, it is the most potent inhibitor of activation of complement, inhibit-

ing all pathways of complement. The primary structure of human CR1 contains an extracellular (1980 residues), transmembrane (25 residues) and a cytoplasmic (43 residues) domain [69,70]. Activity of the normal CR1 molecule is confined to the cell surface of certain cell types. For application as a systemic inhibitor, a soluble version of recombinant human CR1 (sCR1) lacking the transmembrane and cytoplasmatic domains was produced and shown to retain the inhibitory functions of native CR1 [71,72]. Administration of sCR1 in rats exposed to ischemia-reperfusion injury of the heart limited the extent of myocardial tissue injury, and also limited deposition of MAC [71,72]. Furthermore, infiltration of leukocytes in the ischemic area was also significantly attenuated as compared to control animals [71,72]. These results were confirmed in another study [73]. Furthermore, hemodynamic variables, like post-ischemic contractile function, were also improved after reperfusion under administration of sCR1 [73].

Inhibition of C5 activation is another therapeutic option, since this approach prevents formation of the most inflammatory agents C5a and MAC that are generated during complement activation. Vakeva et al. indeed developed an antibody that inhibits activation of C5. In myocardial ischemia/reperfusion experiments, this mAb was shown to significantly inhibit infarct size, myocardial injury and PMN infiltration. Interestingly, this was accompanied by less apoptosis in the ischemic area [74]. Also, an antibody specifically inhibiting the activity of C5a was developed. Hemodynamic parameters and the extent of tissue injury (necrosis) were influenced positively by this inhibitor in ischemia/reperfusion experiments [17]. As expected, deposition of the MAC was not inhibited by anti-C5a, in line with its specificity. The anti-C5a also inhibited (in vitro) neutrophil cytotoxic activity but not neutrophil accumulation in the ischemic area, indicating that factors other than C5a contribute to this phenomena [17].

C1 esterase inhibitor (C1-INH) is a main inhibitor of the classical pathway. It is the only known inhibitor of the serine proteinases C1s and C1r (see review by Caliezi et al. [75]). Moreover, C1-INH presumably inhibits the MBL-pathway as well by inhibiting MBL associated serine proteinases. In addition, C1-INH is an important regulator of the intrinsic pathway of coagulation. Hence, among complement inhibitors, C1-INH is unique in that it inhibits other inflammatory systems as well. Moreover, this inhibitor does not impair the alternative pathway, and does not prevent all defense functions of complement. Buerke et al. showed that C1-INH significantly reduced infarct size in an ischemia/reperfusion model in cats. Contractility of the heart was improved as compared to control animals. Furthermore, PMN accumulation was also shown to be reduced in the ischemic area [76]. Intracoronary C1-INH treatment during ischemia/reperfusion reduced circulating C3 and slightly attenuated C5a plasma concentrations. This was accompanied by a reduction in markers of myocardial cellular injury like creatine kinase and troponine T. C1-INH had no effect of global hemodynamic parameters, but local myocardial contractility was markedly improved in the ischemic zone [23]. In our own studies, we have observed beneficial effects of C1-INH (reduction of infarction size by up to 40%) in a dog model for AMI, not only in ischemia/reperfusion, but under conditions of permanent occlusion (Kleine et al., manuscript submitted).

All studies discussed above show that inhibition of the complement system may markedly improve myocardial damage during AMI, highlighting the detrimental role of this system in this disease. Unfortunately, only limited data are available regarding a potentially detrimental role for complement inhibition in formation of scar tissue in the heart, since interference with this formation would limit the clinical use of complement inhibitors in AMI. In one study, CoVF was shown to reduce slightly the ventricle wall thickness of the infarcted area in rats at 3 weeks after the induction of AMI [65]. Regarding C1-INH, we found no effect of treatment in dogs 3 months after AMI (Kleine et al., manuscript submitted). In a limited clinical trial with C1-INH in patients with AMI, we observed promising effects regarding infarction size (Hermens et al., manuscript in preparation).

5. Initiating complement activation in AMI

Several possible culprits initiating the activation of complement in AMI have been studied. After loss

of integrity of the cell membrane during ischemia/reperfusion, cytosolic components of the cell are exposed to the exterior and, amongst others, may interact with complement proteins. Mitochondria, abundantly present in cardiomyocytes, contain several specific molecules that are able to interact with C1q resulting in activation of the system [77]. Ammonia, released by red blood cells in ischemic conditions, can disrupt the C3 thiolester bond and activate the complement system by increasing the concentration of "C3b-like C3" [78].

In vitro, plasmin can activate C1 with subsequent activation of the entire complement cascade as well as C3 and C5 [79–81]. Thrombolytic agents like (recombinant) tissue-type plasminogen activator (rt-PA) and streptokinase generate plasmin by cleaving plasminogen. Bennet et al. studied the effect of rtPA in six patients with complete coronary occlusion [25]. Compared to the controls with patent coronary arteries (as shown by arteriography), there was a striking increase in circulating anaphylatoxins in the treated group. Streptokinase (SK) and rt-PA induced similar increases in plasma C4a in patients suffering from AMI, whereas levels of C3a and soluble MAC were significantly higher upon administration of SK [26]. In a recent study by our group (manuscript submitted), circulating levels of various complement activation fragments were higher during the first 12 h in AMI patients treated with thrombolysis, as compared to those treated by direct angioplasty. The significance of the rt-PA- or streptokinase-induced complement activation with respect to the extent of ischemic injury remains to be determined, but it is conceivable that the anaphylatoxin release might limit the otherwise beneficial effects of these thrombolytic agents.

Recently, in rat ischemia/reperfusion experiments, C4 and MBL were found to be deposited in the ischemic area at risk, contrary to rat hearts subjected to ischemia only [18]. The molecular mechanisms involved in this MBL pathway activation remain to be established. Interestingly, MBL also specifically binds to endothelial cells exposed to ischemic-reperfusion conditions, but not to cells exposed to ischemia alone in human AMI [18].

Taken together, multiple molecular mechanisms probably contribute to the activation of complement during AMI. Which of these mechanisms play a role in human AMI is not clear. Our own studies point to an important role of yet another mechanism, that is involving the acute phase protein C-reactive protein (CRP).

6. CRP, another culprit?

CRP, a member of the pentraxin protein family, constitutes a cardiovascular risk factor: levels in healthy persons or patients with stable or unstable angina pectoris are associated with the incidence of cardiovascular events [82–85]. In addition, the course of CRP following acute myocardial infarction is associated with the development of complications and with outcome [86,87]. These associations between CRP and cardiovascular events indicate that CRP, by virtue of its acute phase behaviour, is an indirect measure of the degree of inflammation ensuing in atherosclerotic lesions or in the infarcted myocardium. However, as in vitro and in vivo studies have shown, CRP has the ability to activate complement via the classical pathway [88–90]. Therefore, an intriguing possibility is that CRP can bind to jeopardized cardiomyocytes and stimulate complement activation.

Indeed, immunohistochemical studies show the co-localization of CRP and activated complement fragments in infarcted, but not in normal, myocardium of patients whom had died from AMI [20]. CRP depositions in ischemic myocardium has been shown in a rabbit model for AMI as early as 1963, although its association with activated complement was not determined before [91]. These results strongly imply CRP as a main activator of complement in human AMI. Two studies further support this notion. First, human CRP, in a rat model for myocardial infarction, was recently shown to significantly enhance infarct size by activation of complement [92]. Second, in a recent study we measured CRP-C3d and CRP-C4d complexes, activation products that specifically reflect CRP-dependent complement activation, in serial plasma samples of patients with AMI or unstable angina pectoris (UAP), as well as in myocardial tissue homogenates from patients that had died within 14 days after the onset of AMI. Circulating levels of CRP-complement complexes were significantly higher in patients with AMI compared to those in normal controls or in patients with UAP,

and correlated with infarction size as measured by cumulative 48-h LDH release. The increase of CRP-complement complexes in the patients with AMI started at 8–12 h after onset of complaints. This is in agreement with the observation that this is approximately the time that the most early depositions of CRP and complement occur in the ischemic myocardium. Examples of the course of these CRP-complexes in plasma and that of overall complement activation are shown in Fig. 1. The time course of CRP deposition in relation to that of complement and to the expression of ICAM-1 is shown in Fig. 2. Significantly increased levels of CRP-complement complexes were also found in tissue homogenates from the infarcted sites of patients that died from AMI between 12 h and 2 weeks after the onset of symptoms, as compared to levels in the homogenates from non-infarcted sites of the same patients. In addition, levels of these complexes in the infarcted sites correlated with overall complement activation as measured by assays for C4b/c and C3b/c (manuscript submitted). These data indicate that complement activation in infarcted myocardium in humans is predominantly mediated by CRP. Notably, most of the patients included in the study just mentioned had not received reperfusion therapy. Thus, it remains to be established to what extent complement activation induced by reperfusion of the ischemic hearts in human also involves CRP, or whether other mechanisms contribute to this activation as well.

In vitro CRP is able to activate complement after binding to a suitable ligand. CRP can bind to phosphatidylcholine vesicles containing lyso-phophatidylcholine [93]. Lysophopholipids are generated from phopholipids by phopholipase A_2 (PLA_2) enzymes and have been demonstrated in infarcted myocardium [94]. We hypothesized that the presence of lysophopholipids, generated from phospholipids by $sPLA_2$ (or $cPLA_2$), may be involved in the formation of suitable ligands for CRP in the membranes of reversibly injured cardiomyocytes [95]. Remarkably, $sPLA_2$ cannot hydrolyse the phospholipids in the outer leaflet of normal cells but easily hydrolyse those of a flip-flopped cell [96,97]. Thus, this feature of $sPLA_2$ will target the action of CRP to injured (flip-flopped) cells, and not to normal cells. Circulating levels of $sPLA_2$, as CRP, are associated with an increased risk for cardiovascular events [98]. This may point to a common pathogenic pathway. We have found (manuscript submitted) a significant elevation of circulating $sPLA_2$ (starting at 6 h after AMI) preceding that of CRP (present at 12 h), in patients with AMI. Furthermore, our immunohistochemical analysis revealed that depositions of $sPLA_2$ in the infarcted myocardium were more extensive than those of CRP, and occurred partly in areas adjacent to the infarcted area, which contained cardiomyocytes with a normal morphology. However, binding of $sPLA_2$ to the normal cardiomyocytes was not observed in the controlled tissue samples, implying that the apparently normal cardiomyocytes of the areas adjacent to the infarction area that bound $sPLA_2$ presumably were not healthy but may represent a reversibly injured population. Altogether, our findings strengthen our hypothesized role for $sPLA_2$ as an inducer of ligands binding CRP, and as an enhancer of inflammation.

7. Conclusion

Following AMI, ischemia-induced inflammatory reactions involving inflammatory cells, cytokines, complement factors and acute phase proteins ensue in the heart. Complement has been established as a key mediator in these reactions, and at least in animal models, contributes to subsequent tissue damage. Here we have gathered several studies supporting the hypothesis that ligand-bound CRP plays a central role in the inflammatory cascade ensuing in the ischemic heart by activating complement. Future studies should reveal whether this effect of CRP explains that the level of this protein in the circulation constitutes a risk factor for the development of cardiovascular events, and whether CRP-dependent complement activation is a potential target for therapy in patients with AMI.

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