

C-reactive protein

Properties and biological action with particular reference to systemic lupus erythematosus

C. M. MACFARLANE

Summary

A dramatic increase in serum C-reactive protein levels occurs in response to specific bacterial infection or tissue damage. This protein forms part of the acute-phase response, and it appears to function as an independent but relatively nonspecific part of the immune response. It has many properties in common with specific IgG. Absence of an adequate C-reactive protein response may play a role in the pathogenesis of systemic lupus erythematosus.

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This short review has been based largely on the recent extensive reviews of Gewurz *et al.*,¹ Gewurz² and Pepys and Baltz.³ Some of the arguments may be somewhat teleological, but if interest in an important area of intensive current clinical research is stimulated it will have been worth while.

The acute-phase response

The term 'acute-phase response' is generally used to describe the increase in specific serum protein levels following infection, tissue injury and/or inflammation. This response occurs in most vertebrates several hours after cellular insult, and a biological role for many of these acute-phase proteins has been described (Table I). The acute-phase proteins would seem to represent a circulatory scavenger system and act to limit immune response and cellular damage during inflammation. Under non-pathological conditions they may play a role in normal cell regeneration. The increase in most of these proteins is fairly modest (< 10-fold), but increases of over 1 000-fold in C-reactive protein (CRP) levels are commonly found in patients who have experienced bacterial infections, myocardial infarction and surgical trauma. The acute-phase response occurs after the onset of inflammation but before synthesis of specific IgG, and the CRP response must be seen as an important late-phase component of the normal inflammatory response.

Structure, properties and origin of CRP

Knowledge of CRP originated with the observation by Tillet and Francis⁴ in 1930 that sera from patients with febrile disease precipitated with a C-polysaccharide (CPS) extracted from pneumococcus. The substance responsible was a protein

Department of Chemical Pathology, Tygerberg Hospital, Parowvallei, CP
C. M. MACFARLANE, PH.D.

Reprint requests to: Dr C. M. Macfarlane, Dept of Chemical Pathology, Tygerberg Hospital, PO Box 63, Tygerberg, 7505 RSA.

TABLE I. SOME ACUTE-PHASE PROTEINS

	Protein	Biological function
Coagulation proteins	Prothrombin, plasminogen, fibrin	Coagulation
Transport proteins	Ceruloplasmin, ferritin, haemopexin	Regulation of superoxide concentration, copper/iron transport
Protease inhibitors	Haptoglobin α_1 -antitrypsin, α_1 -antichymotrypsin	Haemoglobin scavenger Protease inhibition (collagenase, elastase), inactivated by superoxide products
	α_1 -acid-glycoprotein	Modifies inflammatory response
	Complement proteins	Modulates inflammatory response
	Fibronectin	Modulates phagocytic activity, binds to collagen
	C-reactive protein	Activates classic complement pathway, interacts with lymphocytes
	Amyloid proteins	Unknown, increased in reactive systemic amyloidosis

subsequently shown to be useful as a marker for a broad spectrum of disease.⁵ It was originally thought to be absent from normal plasma,⁵ but sensitive assay techniques have shown that it is a trace constituent of normal plasma which increases dramatically on exposure to inflammatory stimuli. CRP is regarded as a nonspecific but more sensitive indicator of inflammation than the erythrocyte sedimentation rate (ESR).⁶ It increases from approximately 100 ng/ml in neonates to approximately 500 - 1 800 ng/ml in healthy adults,^{1,7} and in the acute phase of disease it can increase 1 000-fold in 2 days.

Human CRP is a cyclic pentamer (pentaxin) of five identical subunits each with a single disulphide bond. It has a molecular weight of 110 000 daltons and no detectable carbohydrate or lipid components.² The complete amino acid sequence is known.⁸ It is synthesized in hepatocytes³ and the increase in the acute-phase response represents largely *de novo* synthesis on stimulation by an extrinsic factor, interleukin I, possibly released from macrophages.³ Patients with liver disease, such as alcoholic hepatitis, show only moderate (< 5-fold) increases in CRP levels.⁹ In rabbits the half-life of CRP in the circulation is 4 - 6 hours.¹⁰

Binding properties of CRP

Binding of CRP to CPS is calcium-dependent ($\geq 0,9$ mM)² and has been shown to involve attachment to monophosphate

ester groups, particularly to the phosphocholine (PC) residues esterified to the galactosamine component of CPS.¹ The affinity of this binding is similar to that found in antibody-antigen interactions (association constant = $1,2 \times 10^5 \text{M}^{-1}$).¹¹ CRP also binds to galactose and galactosamine residues and possesses binding sites for calcium and polyions, e.g. histones, DNA, chondroitin sulphate. The binding of polyions is inhibited by calcium ions (0,1 - 0,5 mM) and is reactivated in the presence of PC residues.¹²

The binding of calcium, polyions or charged lipids^{13,14} induces structural changes in CRP, increases CRP binding to PC residues, and gives rise to what may be termed biologically active CRP. CRP immobilized on a solid phase binds to isolated low-density and very-low-density lipoproteins¹⁵ and CRP *in vivo* activates complement¹⁶ through the classic pathway in the presence of complement component C1q.¹⁷ This complement activation increases opsonic activity and increases clearance of CRP immune complexes through the reticulo-endothelial system of the spleen rather than through the liver.¹⁸

CRP does not bind to normal healthy cells, but it is thought that exposure of the phosphatidylcholine and sphingomyelin in damaged cells and binding of activated CRP to these may lead to complement activation, phagocytosis and splenic clearance of the CRP complexes.¹⁹ Deposits of CRP immune complexes at sites of tissue injury are not as great as would be expected, although they have been demonstrated. However, they do not accumulate at sites of tissue damage to the same extent as do IgG immune complexes.^{1,2}

Activated CRP also binds to certain bacteria and to a subset of large granular lymphocytes containing IgG-FcR receptors (natural killer cells),¹ and modified CRP (but not CRP-CPS complexes) has been shown to promote platelet activation through an active process requiring adenosine triphosphate and calcium.²⁰

CRP therefore possesses many properties in common with IgG, although the recognition capacity is less specific. The ubiquitous presence of phosphatidylcholine and sphingomyelin in cell membranes,²¹ and a possible increase in their accessibility, or in that of other charged phospholipids, on cell injury is consistent with the suggestion that CRP may have a role as a nonspecific circulatory scavenger in diseases involving cellular damage.¹⁹

CRP levels in clinical practice

CRP is useful not only as a nonspecific marker for infection, neoplasia, myocardial infarction and trauma, but it also helps in the differential diagnosis of certain conditions,^{1,3,9} such as systemic lupus erythematosus (SLE) v. rheumatoid arthritis, bacterial v. viral infection, or ulcerative colitis v. Crohn's disease. This has been possible because of the introduction of simple, quantitative analytical procedures for CRP.⁷ The levels of CRP depend on the duration rather than the rate of synthesis by hepatocytes, and in certain diseases, such as rheumatoid arthritis, levels of CRP determined after serial sampling from a single patient may be used as an indication of the severity of the disease and response to treatment.^{3,7} The decrease in CRP on treatment with gold or penicillamine is secondary to control of the primary inflammatory process.³ CRP levels have also proved useful in the diagnosis of bacterial meningitis²² and septicaemia²³ in neonates, in the detection of postoperative infection and secondary infection in SLE²⁴ and in monitoring the success of renal transplants.³ CRP levels are not increased in gastro-enteritis and ulcerative colitis, but may be useful in the differentiation of patients with upper and lower urinary tract infections.^{25,26}

CRP levels in SLE

Certain diseases associated with cellular necrosis show only modest elevation (2 - 4-fold) of CRP levels during the acute phase, e.g. SLE^{24,27} and leukaemias.³ This may be genetically determined, or may be due to the inability to produce and maintain CRP synthesis on stimulation by interleukin I, or to a defect in interleukin production.³ CRP levels in patients with SLE show an increase when secondary bacterial infection is present.²⁴ Therefore at least part of the basic synthetic and secretory mechanisms responsible for CRP production and part of the binding characteristics are intact. Also, animal models (NZB/W mice) for SLE respond to injections of casein and lipopolysaccharides with production of CRP, but fail to show increased CRP levels with progress of the disease.²⁸

The reason for the modest response of CRP in the active phase of SLE therefore remains obscure. Nevertheless, it is felt that the lack of a marked CRP response in SLE may contribute to its progression.^{3,24} It is thought that products released from damaged cells are normally cleared from the circulation by interaction with CRP and other acute-phase proteins. If this response is deficient, it would allow a specific IgG response to be induced against partially modified cellular products released from damaged cells, e.g. DNA, histones and red blood cell components. These IgG antibodies may be serologically polymorphic and directed towards epitopes containing a particular arrangement of phosphate groups.²⁹ (This is not dissimilar to the binding requirement of CRP, i.e. PC phosphate ester residues.) This IgG response may sensitize the individual to further exposure to altered cell components. While CRP complexes are not grossly deposited at sites of cellular damage or inflammation, possibly because of increased splenic clearance, IgG immune complexes are, and deposits of these in the kidney are thought to be the major cause of morbidity in SLE.³⁰ The absence of an adequate acute-phase response in SLE patients may therefore contribute to the development of this chronic, progressive disease.^{3,24}

Studies directed at controlling CRP levels to prevent progression of erosive disease are in progress. Initial reports³¹ that CRP inhibits production of T lymphocytes have subsequently been shown to be incorrect.^{1,32} A deficiency of suppressor T-lymphocyte activity does parallel disease activity in many SLE patients, but this may be secondary to the disease process.³³ It has also been reported that in certain types of SLE there is an inherited deficiency of complement components, including Clq³⁴ which is necessary for CRP-mediated complement activation.¹⁷

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Acute myocardial infarction with normal coronary arteries — viral myopericarditis and possible coronary vasospasm

A case report

T. H. DIAMOND, P. LOTZOF, F. ZIADY

Summary

A young man with normal coronary arteries presented with a transmural apical myocardial infarction. This diagnosis was based on elevated serial cardiac enzyme values, ECG changes, exercise scanning with thallium-201, left ventricular angiography and selective coronary arteriography. Some of the pathophysiological mechanisms implicated in myocardial infarction in patients with normal coronary arteries are discussed and the probable diagnosis of a virus-induced myopericarditis together with coronary artery vasospasm is favoured.

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Case report

A 22-year-old man presented with a history suggestive of angina. He had been well until 2 days before admission to hospital, when he experienced a prodrome of fever, myalgia and sweating, followed by a severe retrosternal 'pressing' chest pain during physical training. He was a non-smoker and there were no other risk factors for atherosclerosis.

On examination the patient was pyrexial, temperature 38°C. Blood pressure, pulse rate, peripheral perfusion and results of cardiac examination were normal. A full blood count showed a leucocytosis of 12,9 x 10⁹/l with a predominant lymphocytosis and atypical lymphocytes. Serial cardiac enzyme values indicated myocardial necrosis with a peak creatine kinase level of 1 550 IU/l (normal 190 IU/l) and a CK-MB fraction of 12%. Serum urea and electrolyte values, uric acid and blood sugar levels and a fasting lipogram were normal. Tests for autoimmune disease were negative. Antibody titres to influenza virus were elevated. A chest radiograph was normal.

The first ECG (Fig. 1) showed features of an acute apical myocardial infarction, with a sinus rhythm of 70/min. The mean QRS frontal axis was -30° and there was a left anterior hemiblock. Loss of R wave and deep, wide Q waves were evident in standard leads III and AVF. There was concave

Department of Internal Medicine, 1 Military Hospital, Voortrekkerhoogte

T. H. DIAMOND, M.B. B.CH., M.R.C.P.

P. LOTZOF, M.B. B.CH.

F. ZIADY, M.D., F.R.C.P., F.C.P. (S.A.)