

Z Gerontol Geriat
 DOI 10.1007/s00391-015-0938-4
 Received: 5 April 2015
 Accepted: 7 July 2015

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C-reactive protein and the acute phase reaction in geriatric patients

Discovery, structure and function of C-reactive protein

In 1930 Tillet and Francis described the finding of a precipitation reaction between the serum of pneumonia patients and the somatic C-polysaccharide of pneumococci [46] and 11 years later Abernethy and Avery isolated the substance responsible for the precipitation and classified this precipitation factor as a protein [1]. Since that time this protein has been called C-reactive protein (CRP) on account of its reactivity with the C-polysaccharide of pneumococci. In 1977 the primary structure of CRP was demonstrated [35]. The amino acid sequence of this non-glycosylated molecule is coded on the long arm of chromosome 1 (1q23.2). This molecule appears to be so important for the body that no functionally relevant genetic defects have been described to date in humans. The intact molecule (molecular mass 115,135 Dalton) consists of five subunits (monomers) (■ Fig. 1). Another molecule with this so-called pentameric structure is serum amyloid P (SAP). This is the CRP equivalent, i.e. the main reactant of the acute phase re-

action, in phylogenetically primitive animals, such as the horseshoe crab and also in representatives of mammals, for example mice [38]. In humans SAP is constitutionally present but is not included in the acute phase proteins [39]. Because of their structural and therefore functional relationship CRP and SAP are included in the family of pentaxins [15]. In special binding domains of the monomers a large group of endogenous and exogenous ligands, such as phospholipids, nuclear ribonucleic acid and histones can be bound and inactivated [14, 16, 51]. After binding to the ligands, the molecule is also able to bind to components of the complement system such as C1q in a calcium-dependent reaction and activate the classical complement metabolic pathway through factor C3. This leads to the precipitation of bacterial pathogens, such as pneumococci and initiate lysis of the pathogens by forming the terminal C5-C9 membrane attack complex [32, 50]. Besides the complement fixation to the pathogens with subsequent lysis or complement-mediated uptake into phagocytes, CRP also causes binding of the CRP-bacteria complex to the Fc receptors of leukocytes because of its immunoglobulin-like protein domains [6, 31, 47] with subsequent activation of cytotoxicity mediated by leukocyte components (e.g.

cytokines and proteases). The molecular function is derived from its properties. It is one of the most important reactants of what is known as the acute phase reaction.

The acute phase reaction is the body's nonspecific reaction triggered by local or generalized tissue damage due to infectious, chemical or physical causes, ischemic necrosis, malignant neoplasms and immunological and allergic reactions. It is clinically characterized by local reactions, such as erythema, swelling and pain. Generalized reactions include malaise, fever and leukocytosis. The purpose of the

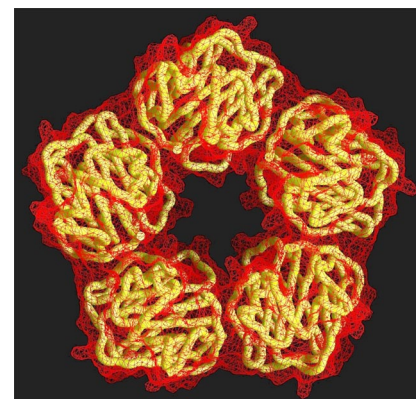


Fig. 1 ▲ Model of the C-reactive protein molecule consisting of five monomers (courtesy of T.J. Greenhough and coworkers, Keele University UK. Image copyright Keele University) [42]

Thomas Bertsch and Jakob Triebel contributed equally to this article.

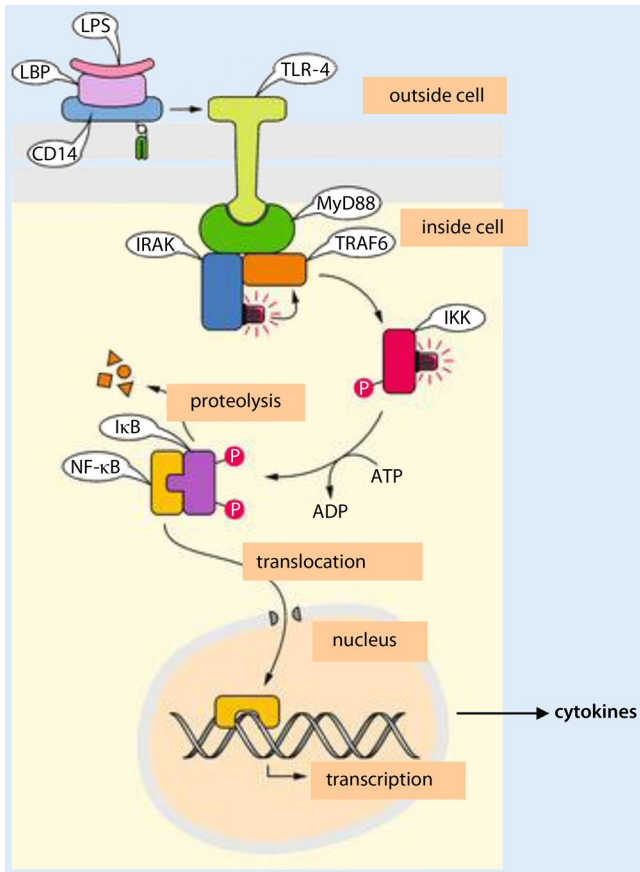


Fig. 2 ▲ Induction pathway to cytokine synthesis via the cluster of differentiation 14 (CD14) receptor and toll-like receptor 4 (TLR-4). Activation of nuclear factor kappaB (NF-κB) via TLR. The ternary complex consisting of lipopolysaccharide (LPS), lipopolysaccharide-binding protein (LBP) and CD14 activates TLR-4 which recruits the myeloid differentiation primary response protein (MYD88). This is followed by an activation of interleukin-1 receptor-associated kinase (IRAK), TNF-receptor associated factor (TRAF6) and Iκkinase (IKK). Activated IKK phosphorylates IκB (inhibitor of NF-κB) which dissociates from the complex with NF-κB. NF-κB diffuses into the nucleus and activates gene promoters [33] (reprinted with kind permission of Springer Science+Business Media).

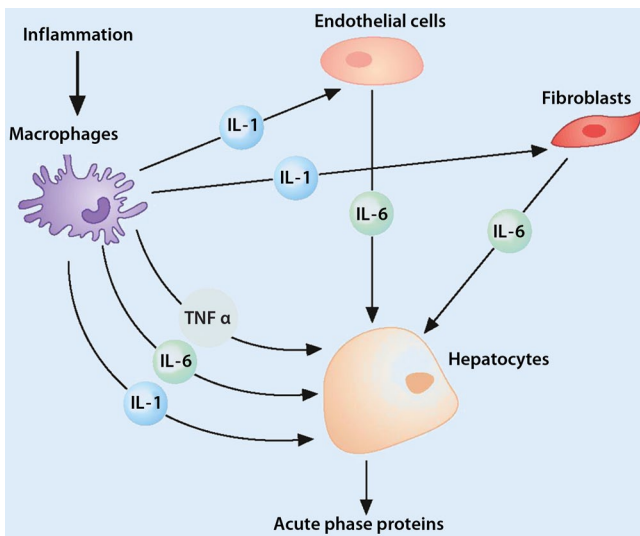


Fig. 3 ◀ The systemic action of the cytokines interleukin 1 (IL-1), IL-6 and tumor necrosis factor alpha (TNF-α) in the induction of acute phase proteins such as C-reactive protein (CRP) [20] (reprinted with kind permission of Springer Science+Business Media)

acute phase reaction is to limit the damage locally and prepare the body for a spread of the damage by a generalized reaction. To fulfil this task, various biochemical reactions take place in the body. How the body deals with the pathogens of a bacterial infection can be used to illustrate the biochemical sequence of an acute phase reaction. Following entry of the pathogens, the bacterial lipopolysaccharides are recognized by the monocyte-macrophage system. The bacterial lipopolysaccharides become associated with lipopolysaccharide-binding protein, which is produced by the liver. The complex of lipopolysaccharide and lipopolysaccharide-binding protein is then bound to the endotoxin receptor CD14 (cluster of differentiation, CD14). This complex then reacts on the cell surface with the toll-like receptors (TLR) and here especially with TLR-4. The TLR family plays an important part in the innate immune response, which is concerned with the rapid and effective elimination of pathogens. The innate immune system contrasts with the specific immune system, which only responds after a few days following exposure to the pathogen, e.g. by production of specific antibodies. Activation of TLR-4 now leads via an intracellular signaling cascade to transcription and translation of the genes for tumor necrosis factor alpha (TNF-α), interleukin-1β and interleukin-6 (IL-6) (■ Fig. 2). An article by Rossol et al. provides a good overview of these mechanisms [40]. The cytokines reach the liver through the circulation where they induce synthesis of acute phase proteins in the hepatocytes, which are released into the circulation (■ Fig. 3). In this process the plasma concentration of CRP, which is an important representative of the acute phase proteins, can rise to 10,000 times the normal concentration. These cytokines, however, also cause activation of various other cell systems in the organism, such as endothelial cells with subsequent release of interleukin 6 (IL-6) (■ Fig. 3) to provide the body with optimal conditions for dealing with the pathogens.

Although initiation of the acute phase reaction in humans, e.g. by bacterial pathogens, leads to a rise in the most varied, reciprocally inhibiting or reinforcing cytokine mediators, studies have shown

that IL-6 is able to induce CRP synthesis without synergy with other mediators. This was demonstrated in a study in which IL-6 was tested as a thrombopoiesis-stimulating medication. Patients were subcutaneously injected with this protein in the form of a recombinant drug prior to chemotherapy to shorten the duration of chemotherapy-induced thrombocytopenia [3]. After treatment with recombinant human IL-6, a rise of the CRP was apparent as a side effect of the cytokine therapy. The serum concentration of TNF- α remained unchanged during the IL-6 treatment, rendering synergy between TNF- α and IL-6 in the induction of CRP synthesis unlikely in this special situation [3, 5].

Time kinetics and diagnostic significance of CRP

Tissue trauma and microbial infections are important initiators of the acute phase reaction. The postoperative period is an example of the high clinical value of CRP measurements, when tissue damage with subsequent infection represents an important pathological situation. The CRP increase occurs to remove the cell detritus generated during the operative trauma. This postoperative increase also prepares the nonspecific immune system for potential infections. The CRP time kinetics after surgical trauma is demonstrated in the following by means of data from pediatric cardiac surgery. During the early postoperative phase there is a slight increase within 12 h up to 10 mg/l followed by a sharp increase to CRP values between 100–150 mg/l. The maximum is reached on the second postoperative day. After 3–4 days there is a fall in the CRP level. Deviation from these kinetics can indicate a postoperative complication due to infection [17]. With respect to the time-dependent kinetics, the following can be stated: the liver begins CRP synthesis approximately 6 h after a bacterial infection and the peak concentration in peripheral blood is reached approximately 48 h after the start of the infection [37]. Elimination of the CRP with a half-life of 19 h is by hepatic clearance [23]. This clearance is constant and is not influenced by comorbidities [49] so that the effectiveness of therapeutic measures can be easily monitored.

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C-reactive protein and the acute phase reaction in geriatric patients

Abstract

The C-reactive protein (CRP), first described as a serum component capable of precipitating the C-polysaccharide of pneumococci, is one of the most important proteins because the serum concentration rises in the acute phase reaction. The acute phase reaction is the nonspecific reaction of the body to noxious stimuli of the most varied kinds, such as infections, burns, neoplasms and tissue trauma. The CRP is synthesized in liver parenchymal cells by cytokines which are derived from stimulated leucocytes and released into the circulation. Because of its molecular structure and in synergy with the complement system, it is able to precipitate and/or lyse microorganisms, thereby rendering them harmless. Measurement of the serum CRP concentration can provide important information with respect to the diagnosis and monitoring of treatment. Due to immunosenescence in geriatric patients the synthesis of CRP appears

to be limited to inflammatory stimuli; however, this phenomenon does not appear to be of major clinical relevance. Despite the introduction of new parameters of the acute phase reaction, sometimes with better performance, such as interleukin-6, procalcitonin and the soluble endotoxin receptor sCD14, measurement of CRP for diagnosis and treatment monitoring is still justified even in geriatric patients as testing is rapid, economic and nearly ubiquitously available round the clock. Biochemical markers of the acute phase reaction should always be interpreted together with the clinical picture and their specific limitations.

Keywords

C-reactive protein · Acute phase reaction · Infection · Innate immune response · Geriatrics

C-reaktives Protein und die Akute-Phase-Reaktion bei geriatrischen Patienten

Zusammenfassung

Das C-reaktive Protein (CRP) – erstmals beschrieben als Serumkomponente, welche in der Lage ist, das C-Polysaccharid der Pneumokokken zu präzipitieren – ist eines der wichtigsten Proteine, dessen Serumkonzentration im Rahmen der Akute-Phase-Reaktion ansteigt. Die Akute-Phase-Reaktion ist die unspezifische Reaktion des Körpers auf Noxen verschiedenster Art, wie beispielsweise Infektionen, Verbrennungen, Neoplasien und Gewebstraumen. CRP wird durch Zytokine, die aus stimulierten Leukozyten stammen, in den Leberparenchymzellen synthetisiert und in die Blutzirkulation abgegeben. Dort vermag es u. a. aufgrund seiner Molekülstruktur in Synergie mit dem Komplementsystem Mikroorganismen zu präzipitieren bzw. zu lysieren und damit unschädlich zu machen. Die Messung der CRP-Konzentration im Serum kann wichtige Informationen bezüglich Diagnostik und Therapiemonitoring bereitstellen. Aufgrund der *Immunseneszenz* beim geriatrischen Patienten scheint die CRP-Synthe-

se auf einen inflammatorischen Reiz hin eingeschränkt zu sein. Dieses Phänomen scheint jedoch klinisch nicht von größerer Relevanz zu sein. Damit ist die Messung des CRP auch beim geriatrischen Patienten zur Diagnostik und zum Therapiemonitoring – trotz der Einführung neuer Messgrößen der Akute-Phase-Reaktion mit z. T. besserer Performance, wie Interleukin-6, Procalcitonin und dem löslichen Endotoxinrezeptor sCD14 – aufgrund der schnellen, fast ubiquitär rund um die Uhr verfügbaren ökonomisch günstigen Messmöglichkeiten immer noch berechtigt. Grundsätzlich sollten biochemische Marker der Akute-Phase-Reaktion immer zusammen mit dem klinischen Bild und ihren spezifischen Limitationen interpretiert werden.

Schlüsselwörter

C-reaktives Protein · Akute-Phase-Reaktion · Infektion · Angeborene Immunantwort · Geriatrie

For the sake of completeness it should be noted that CRP synthesis can also be demonstrated extrahepatically, e.g. in microglia [25], lymphocytes [27], alveolar macro-

phages [13] and fat cells [10]; however, this extrahepatic component only minimally contributes to the CRP concentration in the circulation.

Table 1 Suitability of interleukin 6 (IL-6), procalcitonin (PCT) and C-reactive protein (CRP) for different clinical situations (modified after Boenisch et al. [7, 8])

	Interleukin 6 (IL-6)	Procalcitonin (PCT)	C-reactive protein (CRP)	Clinical situation
Early marker	+++	+(+)	– (late)	Infection and sepsis
Bacterial vs. viral infection	+	+++	+	
Prognosis	+++	+	(+)	
Therapeutic success	++	+++	+	Autoimmune disease
Elevated in active disease ^a	++	–	++	
Bacterial superinfection ^a	– (low specificity)	+++	– (low specificity)	
Applicability in the elderly	++ ^b	+++	++ ^b	General
Cost	– (high)	– (high)	+++ (low priced)	
Availability	+	++	+++ (in nearly every laboratory)	

^aDepending on disease and study [2, 7, 8, 9, 11, 18, 24, 26, 34, 41, 44]
^bIndications for altered production in the elderly.

Measurement of CRP is also important in monitoring acute exacerbations of chronic diseases. Proinflammatory cytokines are released from the focus of inflammation, which then reach the liver via the circulation, where they trigger CRP synthesis. For instance, Crohn's disease activity can be detected by measuring the CRP serum concentration. In ulcerative colitis, another chronic inflammatory bowel disease, the rise in CRP concentration is less marked, probably because the inflammation is limited to the mucosa and is not transmural [48].

Measurement of the CRP concentration is suitable not only for monitoring inflammatory disease activity but also for rapidly assessing the success of treatment of inflammatory diseases. In polyarteritis nodosa, an immunological vasculitis, a drop in the CRP in the first days after initiation of immunosuppressive therapy indicates a response to the treatment [22].

Measurements of CRP in geriatric patients

From what has already been described, it is apparent that measurement of the CRP concentration in the circulation is an important component in establishing a diagnosis and monitoring the course of various diseases. Does this also apply for geriatric patients, particularly in view of the ageing immune system? This process of ageing of the immune system is described by the term immunosenescence, which is associated with dysregulation of the im-

mune system. Although functional changes take place in the innate immune system as part of the ageing process, these are less pronounced than in the acquired immune system. Good review articles include those by Desai et al. [12], Gomez et al. [19] and Opal et al. [36].

Larger scale studies, especially prospective studies regarding the relevance of CRP as a biomarker in geriatric patients with an aged immune system are rare but necessary as a recent study has shown that vital parameters, such as body temperature only have limited value for the detection of infections in elderly patients [43]. In a retrospective study Wester et al. investigated 890 patients who had a positive blood culture for *S. pneumoniae* and *E. coli* from 1994–2004 [53]. The patients were divided into 3 age groups: < 65 years (300 patients), 65–84 years (443 patients) and > 85 years (147 patients). In these groups the CRP levels on the day the blood culture was taken were compared 2–3 days later and again 4–7 days later. A statistically significant negative correlation was found between patient age and the CRP level at the first measurement time. The median CRP levels at the first two blood sampling times were significantly higher in the youngest group; however, no statistically significant differences were found in sensitivity related to age. The authors came to the conclusion that a weakened CRP response with increasing age was seen in the study but that this is hardly of clinical relevance. Another study on the value of CRP measurement in pa-

tients of a geriatric clinic was prospectively conducted by Liu et al. for 3 months in patients who were initially hospitalized in the geriatric department as emergency admissions [30]. The study included a total of 232 patients (135 women, mean age 82.6 years, range 70–99 years and 97 men, mean age 82.6 years, range 69–95 years). In 83 patients infections were diagnosed using the criteria of the International Sepsis Definitions Conference. A significant difference in the mean CRP level (21.3 mg/l vs. 150.5 mg/l) was found between patients with and without infections. The optimal sensitivity and specificity values for the diagnosis of a bacterial infection were found at a cut-off value of 60 mg/l (sensitivity 80.7 %, specificity 96 %, positive predictive value 91.9 % and negative predictive value 89.9 %). Higher sensitivity and specificity values were found for the CRP and body temperature measurements than for the leukocyte count and neutrophil count. The authors came to the conclusion that the CRP is a suitable and useful biomarker for predicting bacterial infections in elderly patients. Talebi-Taher et al. investigated 150 consecutive patients, 50 patients with sepsis, 50 patients with severe inflammatory response syndrome (SIRS) and 50 healthy control persons, who were admitted to the emergency department with SIRS or sepsis [45]. The mean age of all study participants was 74.3 years. The CRP, procalcitonin (PCT), IL-6, erythrocyte sedimentation rate (ESR) and leukocyte count were measured on the first day. In the ROC analysis, the greatest area under the curve (AUC) for CRP was found at 0.88 for differentiating between sepsis and SIRS. At the cut-off level of 12 mg/l the sensitivity was 98 %, specificity was 72 %, the positive predictive value was 63.6 % and the negative predictive value was 98.6 %. For differentiating between SIRS and the control group, the IL-6 values demonstrated the best AUC level of 0.75. In a recent meta-analysis, the diagnostic accuracy of the infection marker PCT for identification of systemic bacterial infections in elderly patients was investigated by Lee et al. [29]. Unlike CRP, PCT is produced in many body cells in the case of bacterial infections. The authors found a specificity and sensitivity of 83 % for PCT and for CRP a

sensitivity of 91% but a specificity of only 36%. They also found no evidence of an influence of age on the PCT value in the sense of immunosenescence. The authors concluded from the results that the PCT level might represent a possible marker for excluding sepsis in elderly patients; however, the results should always be interpreted in the clinical context. A general synoptic overview regarding the different humoral markers and effectors of the acute phase reaction is presented in **Table 1**. The question finally arises as to whether the reference ranges for CRP should be adapted for elderly patients. There is evidence for a tendency to higher CRP values in elderly patients, especially those with frailty or chronic infections [52]; however, elderly persons in general tend to demonstrate a greater range within the reference ranges because of individual heterogeneous previous illnesses [28]. Specific questions should be considered with the individual course of laboratory results with awareness of cut-off values from studies rather than being orientated to age-adapted reference ranges.

Conclusion

The studies cited show that despite the introduction and approval of newer diagnostic markers for identifying and monitoring bacterial infections, such as PCT [21], the soluble subtype of the endotoxin receptors CD14 [4] and IL-6 with sometimes better diagnostic validity compared with CRP, measurement of CRP is still justified in geriatric patients because of its low cost and because it is available round the clock in most hospitals. Biochemical markers of the acute phase reaction should always be interpreted together with the clinical picture and their specific limitations.

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Acknowledgement. The CRP image (Fig. 1) was kindly provided by Professor Trevor J. Greenhough.

Compliance with ethical guidelines

Conflict of interest. T. Bertsch, J. Triebel, C. Bollheimer, M. Christ, C. Sieber, K. Fassbender and H.J. Heppner declare that there are no conflicts of interest.

This article does not contain any studies with human or animal subjects.

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