

C-REACTIVE PROTEIN AND ITS IMPLICATIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

C-reactive protein (CRP) is an acute-phase protein known as a biomarker for inflammation. As such, CRP levels have been traditionally used to detect and predict the outcome of infections, inflammatory and necrotic processes and to monitor the efficacy of treatment in these conditions. With the development of high sensitivity assays, CRP has resurfaced as a very strong predictor in cardiovascular disease and as a mediator of atherosclerosis. The Centers for Disease Control and American Heart Association have elaborated guidelines for the use of CRP in the primary prevention setting and in patients with stable coronary disease or acute coronary syndromes. CRP has been used for differentiation between Systemic Lupus Erythematosus activity and infection, in individuals without serositis. More recently, CRP has also elicited interest as a therapeutic option in lupus. Murine lupus models treated with CRP have been reported to present delayed Lupus onset, decreased antibody levels, enhanced survival and reversal of ongoing proteinuria. In this paper, we reviewed the multiple roles of CRP particularly in lupus.

Keywords: Systemic Lupus Erythematosus; C-Reactive Protein; Cardiovascular Disease; Infection; Diagnosis.

Resumo

A proteína C reactiva (PCR) é uma proteína de fase aguda conhecida como biomarcador de inflamação. Como tal, os níveis de PCR têm sido tradicio-

nalmente utilizados para detectar infecções, inflamações ou processos necróticos, avaliar o prognóstico e monitorizar a eficácia do tratamento destas situações. Com o desenvolvimento de técnicas de alta sensibilidade, a PCR ressurgiu como um marcador predictivo de doença cardiovascular e como mediador da aterosclerose. O *Center for Disease Control* e a *American Heart Association* elaboraram *guidelines* para o uso da PCR na prevenção primária e em doentes com doença coronária estável ou síndromes coronárias agudas. A PCR tem sido utilizada para distinguir a actividade do Lúpus Eritematoso Sistémico da infecção, em doentes sem serosite. Mais recentemente a PCR também despertou interesse como uma possível opção terapêutica no lúpus. Em modelos murinos tratados com PCR houve um atraso no início da doença, redução dos níveis de anticorpos, melhoria da sobrevida e regressão da proteinúria. Neste artigo fazemos uma revisão dos múltiplos papéis desempenhados pela PCR, no lúpus em particular.

Palavras-chave: Lúpus Eritematoso Sistémico; Proteína C Reactiva; Doença Cardiovascular; Infecção; Diagnóstico.

Introduction

In 1930, Tillett *et al*¹ identified C-reactive protein (CRP) for the first time in the serum of patients with *Streptococcus pneumoniae* infection. CRP was described as a factor that could precipitate pneumococcal cell wall "C" polysaccharide.¹ For more than sixty years, CRP has been known to be an acute-phase protein and it has been traditionally used as a biomarker for inflammation.² The term "acute-phase" refers to increase in specific serum protein levels following infection, tissue injury and/or inflammation. This takes place in most vertebrates several hours after cellular insult.³ In response to such diverse stimuli as infection and injury, CRP is synthesized in the liver and its serum concentration

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can increase as much as 1000-fold in just two days.⁴ Induction of CRP synthesis in hepatocytes is regulated by pro-inflammatory cytokines, interleukin-6 (IL-6), IL-1 β and tumor necrosis factor- α (TNF- α).⁵ In humans, the gene for CRP, as well as for serum amyloid P component (SAP), another very similar acute phase protein, have been mapped to an interval, 1q23-24, on the long arm of chromosome 1.⁶ CRP belongs to a family of proteins known as pentraxins. These proteins consist of five identical, noncovalently associated ~ 23 kDa protomers, arranged symmetrically around a central pore. Native pentameric CRP can dissociate into monomers (mCRP) in acidic as well as alkaline conditions, and also when exposed to high-to-high urea and/or low calcium concentrations.⁷ This implies that mCRP may expose neo-epitopes, which can elicit immune responses.⁸ However, mCRP levels are difficult to estimate *in vivo*, because unlike CRP, mCRP is expressed on cell membranes rather than in the plasma.⁸ Insight of biologic functions of CRP can be gained by observing which ligands and effector molecules interact with it. CRP binds phosphocholine found in many bacterial species and in eukaryotic membranes.⁹ However, in normal cells, phosphocholine is not accessible to CRP, so CRP can only bind to this molecule in damaged and apoptotic cells.¹⁰ CRP can also bind several nuclear constituents such as chromatin, histones and small nuclear ribonuclearproteins (snRNP), thus it may have a role in recognition and clearance of damaged nuclear material.¹¹ Ligand-bound or aggregated CRP activates the classical complement pathway through direct interaction with C1q. However, classical pathway activation is limited to the initial stage of complement activation, which generates opsonins, C1-C4. There is little activation of late complement proteins C5-C9, so the strong inflammatory responses associated with C5a and the C5-C9 membrane attack complex are limited. CRP also inhibits activation of C5b-9 by the alternative pathway and deposition of C3b and mannan-binding lectin (MBL)-initiated complement cytolysis by the lectin pathway.¹² The net result is that CRP can participate in host defense while limiting potentially damaging inflammatory effects of complement activation. CRP is also capable of interacting with immunoglobulin receptors, Fc γ RI and Fc γ RII, which elicit response from phagocytic cells. Different pathologic processes cause variable increase in serum CRP, which is clinically useful in the differential diagnosis of diseases.

CRP, cardiovascular disease and SLE

Steady state concentration of inflammatory markers such as CRP, SAP, IL-6, soluble intercellular adhesion molecule-1, and P-selectin have shown association to future coronary events in apparently healthy men and women.¹³ This is in accordance with the well-established role of chronic inflammation in the atherosclerotic disease process.¹⁴ It has been demonstrated that individuals with CRP concentrations in the highest quartile are at two to four times higher risk of future myocardial infarction (MI), ischemic stroke, peripheral artery disease and sudden cardiac death compared with those with CRP in the lowest quartile. Based on these findings, the Center for Disease Control of the USA and the American Heart Association issued guidelines for the use of CRP in the primary prevention setting, and in patients with stable coronary disease or acute coronary syndromes.¹⁵

Coronary artery disease (CAD) is the leading cause of death among SLE patients with disease duration of more than five years. Women with SLE aged 35-44 years have a 52-fold increase in the incidence of myocardial infarction compared with healthy women of the same age group.¹⁶ The pathogenesis of cardiovascular disease in this population is multifactorial. It involves traditional cardiovascular risk factors (hypercholesterolemia, diabetes mellitus, obesity, sedentary lifestyle, hypertension and smoking), similar to the general population, and vascular disease secondary to inflammation and antiphospholipid antibodies. Corticosteroid treatment, underlying renal disease and immune dysregulation may also be important.¹⁷ In addition, Nuttall *et al*¹⁸ found women with SLE tend to have an atherogenic lipid profile, characterized by elevated total cholesterol and triglycerides, and small, dense LDL sub fractions, which further accelerate atherosclerosis. These changes were shown to correlate with moderately increased CRP and oxidative damage. Our group has demonstrated a "lupus dyslipoproteinemia" characterized by high levels of triglycerides and low HDL-c in lupus patients without external factors that affect lipid metabolism.¹⁹ Indeed it was confirmed by demonstration of lipoprotein lipase (LPL) inhibition, responsible for triglyceride hydrolysis, in these patients.²⁰ More recently, we described antibodies to LPL strongly associated to CRP in lupus patients.²¹ Corroborating with the role of inflammation in cardiovascular disease in lupus, Tomita *et al*²² reported that

proinflammatory cytokine genes are constitutively overexpressed in the heart of mice with clinical features of SLE. Surprisingly, the cytokines encoded by these genes (IL-1 β , IL-6, IL-10 and gamma interferon) originated from the cardiomyocytes and not from infiltrating mononuclear cells, as conventionally thought.²³ Cardiomyocyte derived proinflammatory cytokines may contribute to high levels of CRP that may be assessed to predict future cardiovascular risk.²²

In the clinical setting, whether high sensitivity CRP (hsCRP) can be used to assess cardiovascular risk in SLE patients is still unclear. While in one study²⁴ no significant difference in CRP levels was seen between patients with carotid plaque and those without it, two other studies found an association between intima-media wall thickness and CRP levels.^{25,26} Plaque and intima-media wall thickness are subclinical measures of cardiovascular disease and strong predictors of future cardiovascular events and mortality.²⁶ A third study supporting the use of hsCRP in lupus patients showed that, in Caucasians, the proportion of patients with hsCRP values in the highest quintile was significantly higher among those who developed vascular events than among those who did not.²⁷

Although, as Roman stated, it is possible that inflammatory markers lose their discriminatory power with respect to cardiovascular outcome among patients with chronic inflammatory diseases²⁴, we believe there is evidence to support hsCRP as an independent predictor of vascular events in patients with SLE. Small yet significant variations in CRP structure, under different pathological conditions, could be useful in the interpretation of altered inflammatory markers in such complex cases.²⁸

CRP in systemic lupus erythematosus

In lupus and in other autoimmune disorders, CRP may have a protective role because of its ability to bind autoantigens and contribute to apoptotic cell clearance.²⁹ Characteristically, in human SLE there is relative failure of the acute phase CRP response during active disease despite evident tissue inflammation.³⁰ It is not completely clear why in contrast to other rheumatic diseases such as rheumatic arthritis (RA), ankylosing spondylitis, and gout, SLE is a disorder of low CRP response, in spite of apparently comparable degree of tissue inflammation.³¹

Table 1. CRP levels in different clinical settings

Clinical setting	CRP concentration increase (mg/L)
Mild inflammation and viral infections	~10-50
Active inflammation and bacterial infection	50-200
Severe infections and trauma	> 200

As previously mentioned, induction of CRP synthesis in hepatocytes is regulated by IL-6, IL-1 β and tumor necrosis factor- α . Liou *et al*³² demonstrated that serum levels of these pro-inflammatory cytokines in patients with newly diagnosed, untreated SLE were significantly higher than in controls. But interestingly, cytokine levels in lupus sera were lower than corresponding cytokines in RA sera ($p < 0.005$). Cytokine levels and serum CRP were not proportionally correlated.³²

To further understand why CRP levels are lower in SLE compared to RA, in a subsequent study, Liou *et al*³³ went on to discover that, in SLE, two different monocyte populations produce CRP-inducing cytokines (IL-6, IL-1 β and TNF- α). They found that one set of monocytes responded only to lipopolysaccharide (LPS) stimulation while the other set responded only when challenged with immune complexes. This is in contrast to homogeneous RA monocytes, which uniformly produced cytokines in response to both LPS and immune complexes.³³

At the genetic level, Russel *et al*³⁰ investigated the role of human CRP gene polymorphisms in CRP levels and their contribution to SLE susceptibility. Five common CRP haplotypes were identified. Two of these, CRP 2 and CRP 4, were associated with lower CRP levels. Moreover, of the two polymorphisms associated with lower CRP levels, the CRP 4 allele was linked with the development of SLE and antinuclear antibodies production.³⁰

In a further attempt to understand the relationship between CRP levels and SLE, autoantibodies to CRP are discussed. Sjöwall *et al*³⁴ investigated patients diagnosed with SLE and autoimmune hepatitis who were also anti-dsDNA antibody positive, as well as patients with Sjögren's Syndrome, RA, Crohn's disease (CD) and Ulcerative Colitis (UC) for serum anti-CRP autoantibodies. Anti-CRP autoantibodies were found in 13 of 27 SLE patients

(48%), but only in 13% of sera from patients with Sjögren's syndrome. No anti-CRP antibodies were found in any of the samples from patients with RA, CD or UC. In a further study, Sjowall *et al*³⁵ collected serial blood samples of 10 SLE patients. Among the samples, 40% contained anti-CRP antibodies and 7 out of 10 patients were positive at least in one occasion during the study period. All patients with active lupus nephritis were positive for anti-CRP at disease flare. Anti-CRP antibody levels correlated with disease activity (SLEDAI scores) and with anti-DNA levels, and inversely correlated with levels of complement factors such as C1q, C3, C4 and lymphocyte counts.³⁵ Similar results were recently published by Figueredo *et al*³⁶ who found that 51% of SLE patients had elevated levels of anti-CRP antibodies compared to 5% of controls. Again increased levels of these antibodies were associated with active nephritis and with lower levels of C3, suggesting complement consumption. The authors thus concluded that anti-CRP antibodies may be implicated in the pathophysiology of SLE, but in their opinion, these antibodies are not a likely cause for the relative failure of CRP response in patients with active SLE. Our group tested 328 SLE patients for the presence of anti-SAP antibodies. Among them anti-CRP antibodies were tested in a random sample of 28 SLE patients (where 62% of patients harbored elevated anti-SAP antibody titers). Elevated anti-CRP antibody titers were detected in 24% of SLE patients. All patients with elevated anti-CRP antibody titers also harbored elevated titers of anti-dsDNA antibodies.³⁷

What is the role of anti-CRP antibodies in SLE? Our group has recently suggested that anti-CRP antibodies, by binding or inactivating a molecule involved in the clearance of apoptotic cells, may serve as the «*perpetuum mobile*» or the promoter of the vicious cycle of autoimmunity in SLE.³⁸ Clearly, more studies regarding the immune dysregulation in SLE are needed to fully explain why CRP levels are not as elevated as they are expected to be in this pathology.

CRP therapy in SLE: increased survival, decreased nephritis treatment

To our knowledge, three studies have so far investigated CRP's beneficial role in SLE. Since CRP is known to clear nuclear antigens and it is relatively deficient in SLE, Du Clos *et al*³⁹, hypothesized that

CRP treatment could modify the course of autoimmune disease by preventing the exposure of nuclear antigens to the immune system. In the first set of experiments, (NZBxNZW)F1 murine lupus models were subjected to either repetitive injections of CRP and chromatin-coated latex beads, chromatin-coated latex beads alone or latex beads (control group). Chromatin was used to stimulate the disease process, as it was perceived as an important factor for continuous antigenic stimulation in SLE. Indeed, the group that received only chromatin-coated beads had the lowest median survival age, whereas the group treated with CRP had the highest median survival age. This difference was statistically significant. The mean IgG levels against DNA, histones, and DNP (a marker of polyclonal B cell activation) also decreased transiently.³⁹

The second study, that was conducted by Szalai *et al*⁴⁰, showed that (NZB/NZW)F1 mice carrying a human CRP transgene (hCRPtg), the development of autoimmune glomerulonephritis and death were delayed. In SLE, renal involvement is a major cause of morbidity and mortality. The explanation for CRP's ability to limit renal damage was that it prevented glomerular and extra-glomerular deposition of immune complexes, and/or enhanced phagocytosis of immune complexes by mesangial cells.

Finally, in a recent study, Rodriguez *et al*⁴¹ reported that a single dose of 200 µg of human-derived CRP significantly improved renal function and survival in lupus prone (NZBxNZW)F1 mice. CRP not only delayed proteinuria onset in a group of mice treated before renal disease onset, but also reversed ongoing proteinuria in another group that received CRP only at a late stage of disease. CRP also prevented and reversed accelerated nephrotoxic nephritis (NTN), which is an immune complex disease in non-autoimmune mice injected with anti-glomerular basement membrane antibody. Interestingly, CRP showed no benefit when used to treat NTN in interleukin-10 (IL-10) deficient mice. This last finding coupled with the fact that CRP produces a long-lasting effect on the autoimmune process led the authors to believe CRP's exerts its protective effect through IL-10 dependent anti-inflammatory process, rather than on continued clearance of antigens as previously thought.⁴¹ As Ogden and Elkon point out, these studies lead us to consider the possibility of using CRP in the treatment of human SLE, but whether it is a safe and ef-

Table II. An overview on how to interpret CRP increases in patients with SLE⁴⁶

Clinical Setting	Median CRP level
SLE flare without serositis	4-16 mg/l, with a range of 0-60 mg/l
SLE with infection	60 and 82 mg/l, with a range of 1-400 mg/l
SLE with active serositis	76 mg/l with a range of 2-375 mg/l

fective therapeutic option still needs to be determined.⁴²

Systemic lupus erythematosus, infection, and CRP

CRP levels above 60 mg/l in febrile SLE patients without serositis almost always indicate infection; whereas in SLE alone, CRP levels are only moderately raised even in patients with very active disease.³¹ CRP is significantly increased in patients suffering from intercurrent infection.⁴³ SLE patients have higher incidence of infection in a Korean study, and the CRP is a marker for infection⁴⁴, which is a major cause of morbidity and mortality in these patients.⁴⁵ This study also found CRP levels were significantly elevated in SLE patients with infection compared to non-infected controls (66mg/l vs. 5.4 mg/l, $p < 0.001$)⁴⁴. Roy *et al*⁴⁶ suggested escalating levels of CRP as predictive of infection or active serositis (see Table II). Hence, measurement of CRP can be helpful in differentiating SLE flares without serositis from infections.

Summary

C-reactive protein (CRP) is an acute-phase protein known as a biomarker for inflammation. Nowadays, the study of this pentraxin has incorporated and discovered many important functions, such as a marker and an active player in atherosclerosis, complement activation and possible therapeutic use in SLE. CRP inappropriate response in lupus' activity continues to be a mystery, but it can favor its future use as a marker of atherosclerosis, since only infections and serositis are the sufficient stimulus for a significantly increase in its serum levels.

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References

1. Tillett W and Francis TJ. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. *J Exp Med* 1930;52:561-571.
2. Gewurz H, Mold C, Siegel J and Fiedel B. C-reactive protein and the acute phase response. *Adv Int Med* 1982;27:345-372.
3. Macfarlane CM. C-reactive protein. Properties and biological action with particular reference to systemic lupus erythematosus. *S Afr Med J* 1985;67:890-892.
4. Kushner I. The acute phase response: an overview. *Methods Enzymol* 1988;163:373-383.
5. Castell JV, Gomez-Lechon MJ, David M, Fabra R, Trullenque R and Heinrich PC. Acute-phase response of human hepatocytes: regulation of acute-phase protein synthesis by interleukin-6. *Hepatology* 1990;12:1179-1186.
6. Walsh MT, Divane A and Whitehead AS. Fine mapping of the human pentraxin gene region on chromosome 1q23. *Immunogenetics* 1996;44:62-69.
7. Potempa LA, Siegel JN, Fiedel BA, Potempa RT and Gewurz H. Expression, detection and assay of a neoantigen (Neo-Crp) associated with a free, human C-reactive protein subunit. *Mol Immunol* 1987;24:531-541.
8. Khreiss T, Jozsef L, Potempa LA and Filep JG. Conformational rearrangement in C-reactive protein is required for proinflammatory actions on human endothelial cells. *Circulation* 2004;109:2016-2022.
9. Volanakis JE and Kaplan MH. Specificity of C-reactive protein for choline phosphate residues of pneumococcal C-polysaccharide. *Proc Soc Exp Biol Med* 1971;136:612-614.
10. Gershov D, Kim S, Brot N and Elkon KB. C-reactive protein binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an antiinflammatory innate immune response: implications for systemic autoimmunity. *J Exp Med* 2000;192:1353-1364.
11. Du Clos TW. C-reactive protein reacts with the U1 small nuclear ribonucleoprotein. *J Immunol* 1989;143:2553-2559.
12. Suankratay C, Mold C, Zhang Y, Potempa LA, Lint TF and Gewurz H. Complement regulation in innate immunity and the acute-phase response: inhibition of mannan-binding lectin-initiated complement cytolysis by C-reactive protein (CRP). *Clin Exp Immunol* 1998;113:353-359.
13. Ridker PM, Stampfer MJ and Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA* 2001; 285: 2481-2485.
14. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med* 1999;340:115-126.
15. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for he-

- althcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499-511.
16. Manzi S, Meilahn EN, Rairie JE, et al. Age-specific incidence rates of myocardial infarction and angina in women with systemic lupus erythematosus: comparison with the Framingham study. *Am J Epidemiol* 1997;145: 408-415.
 17. Manzi S. Systemic lupus erythematosus: a model for atherogenesis? *Rheumatology (Oxford)* 2000;39:353-359.
 18. Nuttall SL, Heaton S, Piper MK, Martin U and Gordon C. Cardiovascular risk in systemic lupus erythematosus—Evidence of increased oxidative stress and dyslipidaemia. *Rheumatology (Oxford)* 2003;42:758-762.
 19. Borba EF and Bonfa E. Dyslipoproteinemias in systemic lupus erythematosus: influence of disease, activity, and anticardiolipin antibodies. *Lupus* 1997;6: 533-539.
 20. Borba EF, Bonfa E, Vinagre CG, Ramires JA and Maranhao RC. Chylomicron metabolism is markedly altered in systemic lupus erythematosus. *Arthritis Rheum* 2000;43:1033-1040.
 21. de Carvalho JF, Borba EF, Viana VS, Bueno C, Leon EP and Bonfa E. Anti-lipoprotein lipase antibodies: a new player in the complex atherosclerotic process in systemic lupus erythematosus? *Arthritis Rheum* 2004;50: 3610-3615.
 22. Tomita M, Dragoman M, Worcester H, Conran P and Santoro TJ. Proinflammatory cytokine genes are constitutively overexpressed in the heart in experimental systemic lupus erythematosus: a brief communication. *Exp Biol Med (Maywood)* 2004;229:971-976.
 23. Wijetunga M and Rockson S. Myocarditis in systemic lupus erythematosus. *Am J Med* 2002;113:419-423.
 24. Roman MJ, Shanker BA, Davis A, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N Engl J Med* 2003;349: 2399-2406.
 25. Doria A, Shoenfeld Y, Wu R, et al. Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. *Ann Rheum Dis* 2003;62:1071-1077.
 26. Selzer F, Sutton-Tyrrell K, Fitzgerald SG, et al. Comparison of risk factors for vascular disease in the carotid artery and aorta in women with systemic lupus erythematosus. *Arthritis Rheum* 2004;50:151-159.
 27. Toloza SM, Uribe AG, McGwin G Jr, et al. Systemic lupus erythematosus in a multiethnic US Cohort (Lumina). XXIII. Baseline predictors of vascular events. *Arthritis Rheum* 2004;50:3947-3957.
 28. Das T, Sen AK, Kempf T, Pramanik SR and Mandal C. Induction of Glycosylation in Human C-Reactive Protein under Different Pathological Conditions. *Biochem J* 2003;373:345-355.
 29. Szalai AJ. C-reactive protein (CRP) and autoimmune disease: facts and conjectures. *Clin Dev Immunol* 2004;11: 221-226.
 30. Russell AI, Cunninghame Graham DS, Shepherd C, et al. Polymorphism at the C-reactive protein locus influences gene expression and predisposes to systemic lupus erythematosus. *Hum Mol Genet* 2004;13:137-147.
 31. ter Borg EJ, Horst G, Limburg PC, van Rijswijk MH and Kallenberg CG. C-reactive protein levels during disease exacerbations and infections in systemic lupus erythematosus: a prospective longitudinal study. *J Rheumatol* 1990;17:1642-1648.
 32. Liou LB. Serum and in Vitro Production of IL-1 Receptor antagonist correlate with C-reactive protein levels in newly diagnosed, untreated lupus patients. *Clin Exp Rheumatol* 2001;19:515-523.
 33. Liou LB. Different Monocyte Reaction patterns in newly diagnosed, untreated rheumatoid arthritis and lupus patients probably confer disparate C-reactive protein levels. *Clin Exp Rheumatol.* 2003;21:437-444.
 34. Sjowall C, Eriksson P, Almer S and Skogh T. Autoantibodies to C-reactive protein is a common finding in SLE, but not in primary Sjogren's syndrome, rheumatoid arthritis or inflammatory bowel disease. *J Autoimmun* 2002;19:155-160.
 35. Sjowall C, Bengtsson AA, Sturfel G and Skogh T. Serum levels of autoantibodies against monomeric C-reactive protein are correlated with disease activity in systemic lupus erythematosus. *Arthritis Res Ther* 2004; 6:R87-R94.
 36. Figueredo MA, Rodriguez A, Ruiz-Yague M, et al. Autoantibodies against c-reactive protein: Clinical associations in systemic lupus erythematosus and primary antiphospholipid syndrome. *J Rheumatol* 2006;33:1980-1986.
 37. Zandman-Goddard G, Blank M, Langevitz P, et al. Anti-serum amyloid P (SAP) antibodies in SLE patients correlate with disease activity. *Ann Rheum Dis* 2005;64: 1698-1702.
 38. Szyper-Kravitz M and Shoenfeld Y. Autoimmunity to protective molecules – is it the perpetuum mobile (vicious cycle) of autoimmune rheumatic diseases? *Nat Clin Pract Rheumatol* 2006;2:481-490.
 39. Du Clos TW, Zlock LT, Hicks PS and Mold C. Decreased autoantibody levels and enhanced survival of (Nzb X Nzw) F1 mice treated with C-reactive protein. *Clinical Immunol Immunopathol* 1994;70:22-27.
 40. Szalai AJ, Weaver CT, McCrory MA, et al. Delayed lupus onset in (Nzb X Nzw)F1 mice expressing a human C-reactive protein transgene. *Arthritis Rheum.* 2003;48:1602-1611.
 41. Rodriguez W, Mold C, Kataranovski M, Hutt J, Marnell LL and Du Clos TW. Reversal of ongoing proteinuria in autoimmune mice by treatment with C-reactive protein. *Arthritis Rheum.* 2005;52(2):642-650.
 42. Ogden CA and Elkon KB. Single-dose therapy for lupus nephritis: C-reactive protein, nature's own dual scavenger and immunosuppressant. *Arthritis Rheum* 2005; 52:378-381.
 43. Becker GJ, Waldburger M, Hughes GR and Pepys MB. Value of serum C-reactive protein measurement in the investigation of fever in systemic lupus erythematosus. *Ann Rheum Dis* 1980;39:50-52.
 44. Suh CH, Jeong YS, Park HC, et al. Risk factors for infection and role of C-reactive protein in Korean patients with systemic lupus erythematosus. *Clin Exp Rheumatol* 2001;19:191-194.
 45. Zandman-Goddard G and Shoenfeld Y. SLE and infections. *Clin Rev Allergy Immunol.* 2003;25:29-40.
 46. Roy S and Tan KT. Pyrexia and normal C-reactive protein (CRP) in patients with systemic lupus erythematosus: always consider the possibility of infection in febrile patients with systemic lupus erythematosus regardless of CRP levels. *Rheumatology (Oxford)* 2001;40:349-350.