ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

C-Reactive Protein: A Novel Inflammatory Biomarker

M R Adak*

Department of Biochemistry, Professor, Anna medical College and Research Center, Solitude, Mauritius.

ABSTRACT

C-reactive protein (CRP) is a positive acute-phase protein that increases in response to both acute and chronic inflammatory response and reaches high peaks in 24 - 48 hours. CRP has received considerable attention as an inflammatory marker and in some cases a contributor to the diagnosis of cardiovascular diseases. Traditionally, CRP has been measured within exercise studies to provide evidence of an acute-phase inflammatory response due to muscle damage. Numerous studies have now shown an inverse relationship between physical activity levels and resting concentrations of CRP. Thus, exercise may prove beneficial in lowering systemic inflammatory markers such as CRP, and consequently contribute towards preventing the progression of inflammatory disorders.

Keywords: C-reactive protein, inflammatory, biomarker

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Serum C-reactive protein (CRP) is a systemic biomarker for diagnosis of acute and chronic inflammation. In 1930, it was isolated from the serum of patients with pneumonia [1]. The extract was originally labeled Fraction C, and was later confirmed as a polysaccharide. The gene for CRP has been localized to chromosome 1 [2] and codes for a mature, 206 amino acid polypeptide [3]. Other acute phase proteins include serum amyloid A (SAA), Alpha-1 acid glycoprotein, alpha-1 anti-trypsin, haptoglobins, ceruloplasmin, fibrinogen, ferritin and complement components C3, C4 [4]. They appear in the peripheral blood in response to infection, trauma, myocardial infarction, inflammatory disease and malignancy. They are produced within a few hours by the liver in response to inflammatory cytokines such as interleukin-1 (IL-1), tumor necrotic factor (TNF) and in particular IL-6 [5].

Acute phase proteins are two classes as per their concentrations in plasma .In some cases acute phase proteins concentration in plasma increase with inflammatory reaction known as positive acute phase proteins. However, some plasma protein concentrations decrease with inflammatory reaction referred as negative phase proteins [6, 7]. Serum CRP has also been found to be elevated in patients with many malignancies, implying a close linkage between inflammation and malignancy. Prospective studies have shown a higher risk of developing cancer in those with elevated serum CRP. CRP is produced by hepatocytes in response to inflammatory cytokines, particularly, interleukin-6 from the tumor microenvironment. CRP synthesis was originally thought to be confined to the liver with no evidence supporting its production in cells other than hepatocytes [8]. Additional extrahepatic sites of CRP synthesis/gene expression have been identified and include the epithelial cells of the human respiratory tract and T-lymphocytes in culture [9].

CRP is a classic member of the pentraxin family, characterized by proteins of a cyclic pentameric structure and calcium dependent ligand binding. Pentraxins play important parts in innate immunity for the opsonization and clearance of microbes and apoptotic cells. Pentraxin 3 (PTX3), a recently identified member, is a long pentraxin and is rapidly produced from the cells involved in atherosclerotic lesions [10].

In inflammatory reactions, CRP levels may rise dramatically in order to facilitate non-specific immune functions and assist with the repair process. The ability of CRP to recognize disease-causing agents and damaged cells and to mediate their removal facilitates the process [11]. The increased CRP was associated with enhanced phagocytosis of the apoptotic cells and would thus contribute towards their clearance. Opsonisation involves coating of the bacterial surface so that it can be recognized by other cells of the immune system, specifically macrophages and neutrophils. Thus, opsonisation by CRP promotes the uptake, and therefore removal of these cells by phagocytes [12]. In the past, CRP has been used to confirm the diagnosis of acute or chronic infections and to evaluate chronic inflammatory diseases, including rheumatoid arthritis, Crohn's disease, and systemic lupus erythematosus. During this decade, the role of serum CRP has been re-emphasized by extending its clinical use to the diagnosis of cardiovascular diseases. CRP also plays an important role in the pathogenesis of

atherosclerosis [13]. Nearly two-thirds of the population has plasma CRP levels fewer than 3 mg/L. Circulating CRP levels under 10 mg/L have historically been regarded as clinically insignificant. During recent years, a number of researchers have demonstrated an association between minor elevated CRP, between 3 and 10 mg/L, and the risk of developing cardiovascular diseases, metabolic syndrome, and cancers [14].

Elevated CRP is most likely a response secondary to tumor necrosis, local tissue damage, and associated inflammation in patients with malignancies [15]. CRP is produced in hepatocytes as a systemic response to cytokines in the blood stream, particularly IL-6, released from leukocytes within tumor microenvironment [16]. IL-6 may also indirectly help the binding of CRP to phospholipids on tumor cells, activating the classic C1q pathway of the complement system and act as an opsonin, which may lead to tumor cell lysis [17]. It is also well established that an acute spell of exercise may alter the circulating levels of a number of pro-inflammatory cells including cytokines, acute-phase proteins and white blood cells [18]. Evidence suggesting a possible role of inflammatory response following exercise may include haemolysis, [19] endotoxaemia, [20] and the production of reactive oxygen species [21].

CRP serves to activate and modulate the first complement C1q through cascade mechanism by enhancing opsonisation and local inflammation [22]. CRP also inhibits the alternate and lectin pathways of complement through the recruitment of factor H, a regulatory protein that promotes the degradation of the C3 and C5 convertase [23]. However, once the CRP has moved into the tissue and reacts with macrophages, inflammation is suppressed through the inhibition of interleukin-1b (IL-1b) and interleukin-1ra (IL- 1ra). Additional anti-inflammatory properties exhibited by CRP include the ability to decrease the expression of cell adhesion molecule (L-selectin) *in vitro*, and reduce neutrophils superoxide production [24].

The production of CRP in hepatocytes is principally induced at the transcriptional level by IL-6, and can be synergistically enhanced by the addition of IL-1 [5]. Following transcriptional factors C/EBP family (CCAAT/enhancer binding protein), STAT3 (signal transducers and activators of transcription), and Rel (v-rel reticuloendotheliosis viral oncogene homologavian) proteins are required for CRP synthesis [25]. The nuclear factor B (NF-B) subunits p50 and p65 through protein kinase C pathway is also involved in cytokine induction of CRP synthesis [26]. The interactions of these transcription factors cause maximal induction of CRP expression in hepatocytes [27].

In **conclusion**, CRP is a positive acute-phase protein that is upregulated in response to injury, infection or antigen exposure. The increased synthesis of CRP occurs largely in the liver and reaches in high peaks 24 - 48 hours after the aggressive stimulus. CRP levels may rise dramatically in order to facilitate non-specific immune functions and assist with the repair process. In last 10 years, the role of serum CRP has been re-emphasized by extending its clinical use to the diagnosis of cardiovascular diseases. The alterations in CRP are also closely related to exercise-induced inflammatory markers following physical activity to muscle damage. CRP is produced in hepatocytes as a systemic response to cytokines in the blood stream, particularly IL-6, released from leukocytes within tumor microenvironment. The nuclear factor B (NF-B)

subunits p50 and p65 through protein kinase C pathway is also involved in cytokine induction of CRP synthesis. Therefore, CRP has long been used as a clinical guide to diagnosis, management, and prognosis. Not only this, but also it can be used to predict a new-onset inflammatory disorder.

REFERENCES

[1] Tillett W S, Francis T. J Exper Med 1930; 52: 561–567.
[2] Whitehead AS, Bruns GAP, Markham AF. Science 1983; 221: 69–71.
[3] Oliveira EB, Gotschlich EC, Liu TY. J Bio Chem 1979; 254: 489–502.
[4] Dhingra R, Gona P, Nam BH, D'Agostino RB, Wilson PWF, et al. Am J Med 2007: 120:1054 - 1062.
[5] Castell JV, Gomez-Lechon MJ, David M, Fabra R, Trullenque R, et al. Hepatotlogy 1990; 12:1179-1186.
[6] MacLeod CM, Avery OT. J Exp Med 1943; 73:183-191.
[7] Gabay C, Kushner I. N Engl J Med 1999; 6:448-454.
[8] Kushner I, Rzewnicki D, Damols D. Am J Med 2006; 119:17-28.
[9] Engwegen JYMN, Helgason HH, Cats A, Harris N, Bonfrer JMG,et al.World J Gastroenterol 2006; 12:1536-1544.
[10] Mantovani A, Garlanda C, Doni A, Bottazzi B . J Clin Immunol 2008; 28:1-3.
[11] Gershov D, Kim S, Brot N, Elkon KB J Exp Med 2000; 192:1353-1364.
[12] Benjamin E, Sunshine G, Leskowitz S . Immunology: A Short Course. New York: Wiley-Liss, 1996.
[13] Jialal I, Devaraj S, Venugopal SK. Hypertension 2004; 44:6-11.
[14] Tolia G M, Kouloulias E V, Pantelakos S P, Syrigos N K. Int J Clin Exp Med 2013; 6:50-56.
[15] Slaviero KA, Clarke SJ, Rivory LP. Lancet Oncol 2003; 224-232.
[16] Canna K, McArdle PA, McMillan DC, McNicol AM,Smith GW, et al. Br J Cancer 2005;92:651-654.
[17] Black S, Kushner I, Samols D . J Bio Chem 2004; 279:48487-48490.
[18] Semple SJ, Smith LL, McKune AJ, Neveling N, Wadee AA . South Afri J Sports Med 2004; 16:17-21.
[19] Lijnen P, Hespel P, Fagard R, et al. Int J Sports Med 1998; 9:108- 113.
[20] Jeukendrup AE, Vet-Joop K, Sturk A, et al. Clin Sci 2000; 98: 47-55.
[21] Ji LL. Exp Bio Med 1999; 222:283-292.
[22] Mold C, Gewurz H, Du-Clos TW. Imm pharma 1999; 42:23-30.
[23] Pue CA, Mortensen RF, Marsh CB, Pope HA, Wewers MD. J Immunol 1996; 156:1594-1600.
[24] Zouki C, Beauchamp M, Baron C, Filep J. J Clin Invest 1997; 100:522-529.
[25] Cha-Molstad H, Young DP, Kushner I, Samols D. Mol Immunol 2007; 44:2933-2942.
[26] Hefler LA, Concin N, Hofstetter G, Marth C, Mustea A, et al. Clin Cancer Res 2008; 14:710-714.
[27] Agrawal A, Samols D, Kushner I. Mol Immunol 2003; 40:373-380.