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C - REACTIVE PROTEIN: AN INFLAMMATORY BIOMARKER PRESENT IN MULTIPLE DISEASE PATHOGENESIS

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ABSTRACT C-reactive protein (CRP) is an acute-phase protein belongs to pentraxins family with a feature of five identical globular subunits. Two different isoforms i.e. pentameric CRP (pCRP) and monomeric CRP (mCRP) have different key role in regulation. The key biological function of CRP is host defense using classical complement pathway against bacterial infection and involved in removal of apoptotic and necrotic cells. Although CRP is mainly associated with inflammation in bacterial infection such as tuberculosis or Pneumococcus infection, however it is also presence in atherosclerosis, cardiovascular disease (CVD) and in various cancers which make it good candidate for prognostic study in different clinical conditions.

KEYWORDS : Complement Pathway, CRP, Host Defense, Inflammation.

1.INTRODUCTION

C-reactive protein is an acute-phase inflammatory plasma protein discovered by Tillet and Francis in 1930, while investigating the patients sera having *Pneumococcus* infection [1]. CRP was named for its capability to precipitate the C-polysaccharide of *Streptococcus pneumoniae*. [2]. CRP binds to phosphocholine (PCh) on microorganisms which is calcium dependent and it activates the classical complement pathway of innate immunity [3]. The average serum concentration of CRP in a healthy individual is 0.8 mg/L, but different factors including polymorphisms in the CRP gene can affect the base line of CRP in individuals [4]. Other factors are age, gender, smoking habit, lipid profile, weight and hypertension, which also can affect the baseline of CRP levels [5].

The pentameric isoform of CRP is synthesized mainly in hepatocytes however other cells are also able to synthesized CRP including macrophages [6], smooth muscles cells [7], adipocytes and lymphocytes [8] and endothelial cells [9]. Monomeric CRP (mCRP) is building block of pentameric CRP (pCRP) and mCRP is assembled to form pCRP in endoplasmic reticulum [10]. CRP is typically considered as critical regulator of the innate immunity and a dominant facilitator of acute-phase response. It is also associated with chronic inflammation in cancer, rheumatologic conditions, tuberculosis and cardiovascular disease [11-13]. CRP protein is primarily synthesized in the liver [14], in response to pro inflammatory cytokines such as IL-6 which seem to be the main regulator for synthesis [15]. The present study summarizes the biological significance and association of CRP with disease pathogenicity in multiple clinical conditions.

2.C - REACTIVE PROTEIN: STRUCTURE AND FUNCTION

Human CRP sequence having 224 amino acids containing signal sequence of 18 amino acid at amino terminal. Mature peptide of CRP contains 206-amino acid which is member of the short pentraxins family with high phylogenetic conservation [16]. Pentraxins family have common structural characteristic including five identical globular subunit and each subunit constituted by two beta pleated sheets that are non-covalently connected and organized in a symmetric cyclic pattern, decisive a pentameric configuration [17, 18]. In circulation, pentameric isoform of CRP (pCRP) is formed and secreted by the liver [19]. In some condition pentameric CRP (pCRP) gone thorough conformational changes to form monomeric CRP (mCRP) and this mCRP is significantly less soluble than pCRP [20]. It was reported that lipids are responsible for the dissociation of pCRP to its monomeric form mCRP. Though the structure and confirmation of mCRP is not clear and it may form dimer or trimer with distorted confirmation [21].

The pCRP termed as native CRP (nCRP), which has five identical globular subunit with discoid configuration. All five subunits are present in same orientation around the central core with two-layered beta sheet [22]. Each globular subunit have phosphocholine (PCh) binding site [23]. The molecule has characteristic feature of having two calcium ions per subunit and the presence of calcium ions are essential for the high stability and binding to PCh. One face of molecule used to interacts with complement pathway molecule C1q and participate in activation of classical complement pathway [24]. The pCRP can be irreversibly dissociated to its monomeric form mCRP and this dissociation was reported in the presence of urea or in the absence of calcium at high temperature [19, 25]. Both form i.e. pCRP and mCRP have different characteristics including antigenic activity and epitope, biological function and its electrophoretic mobility [26]. The mCRP isoform increase the adherence of platelet to neutrophil cells however pCRP reported to decrease the adherence [27]. Both pCRP and mCRP have different affinity for formation of immune complex. The pCRP used to binds to low affinity IgG receptor FcγRIIa while mCRP used to bind Fc RIIIa (CD16a) on monocytes and Fc RIIIb (CD16b) on neutrophils with low affinity immune complex [28].

3.CRP: LIGANDS AND RECEPTORS

Phosphocholine (PCh) is the most well characterized ligand for CRP and this feature is utilizing for purification of protein [17]. Calcium ion is required for the interaction of CRP to PCh of various microorganisms as in case of C -polysaccharide of pneumococcus [29]. PCh is generally not exposed on the cell membrane however in case of membrane damage it exposed because of complement system and available for binding with CRP [30]. Calcium dependent binding of CRP to apoptotic

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cells, increases the binding of C1q and C3b/bi and hence triggered classical complement pathway. This binding enhances the phagocytosis process of apoptotic cells and this process termed as CRP associated anti-inflammatory response [31, 32]. CRP also reported to bind to chromatin through interactions with histones. Binding of CRP to H1 and H2A histone is more prominent than other histone protein H2B, H3 and H4. CRP does not directly bind to DNA [33, 34].

4.CRP DEFENSE MECHANISM

Complement system is one of the important components of innate immune system which enhance the capability of antibodies and phagocytic cells to remove dead cells and microbial cells form the body using either classical or alternative pathways [35]. In defense mechanism, CRP binds to complement system component C1q and trigger classical complement cascade. By classical complement pathway, CRP protects the body by clearing pathogenic bacteria including *H. influenzae* [36] and *S. pneumoniae* [37]. Apart from innate immunity, CRP also has defense mechanism for histone toxicity released in blood circulation after extensive cell mortality. CRP reduces the damage of endothelial cell induced by histone and coagulation activation. CRP interacts with histones and form complex [38].

Convincing indication from different *in vitro* studies reveal the CRP-mediated opsonization of modified forms of LDL via Fc receptors by macrophages [39]. In Atherosclerosis, CRP either in monomeric (mCRP) or in pentameric (pCRP) form regulates activation of complement system in the vessel wall and CRP has protective effects by making modified LDL-CRP complex which activates the complement system [40, 41].

5.CRP IN ATHEROSCLEROSIS PATHOPHYSIOLOGY

Inflammation with the presence of CRP, SAA and fibrinogen are the key factors of pathogenesis of atherosclerosis [42-44]. CRP is reported as sensitive marker of inflammation and its concentration can elicit up to 1000 folds in inflammation [15]. Many studies report that C-reactive protein is an independent biomarker of atherothrombosis [45] and atherosclerosis [46]. Reports suggested that CRP itself plays are crucial role in atherosclerosis pathogenesis [47]. Endothelial dysfunction is the first step which promotes the formation of atherosclerotic plaque and hence inflammation. In case of injury, endothelial cells express adhesion molecules on cell surface including endothelial leukocyte adhesion molecule-1, intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 [48].

Few WBCs including T-cells (Tc and Th cells) and monocytes pass through endothelial cell barrier by diapedesis process. In continuation, LDLs accumulate on the site of injury and in gulp by macrophages which form fatty spot. Further proliferation of smooth muscle cells (SMCs) and component of extracellular matrix form a fibrous cap. This morphological spot is called atherosclerotic lesion [49]. Various mediator molecules including cells (endothelial cells, T cells, SMCs), complement factors, inflammatory proteins (IL1, IL6, TNF and CRP) are contributed to develop this lesion, and eventually cause plaque rupture. In atherosclerosis, CRP may be involved by complement activation, monocyte recruitment, vascular cell activation, apoptosis, and thrombosis [50-53].

6.CRP IN CORONARY HEART DISEASE

Inflammation is well known factor responsible for the pathogenesis of coronary heart disease (CHD). Various clinical studies demonstrated that CRP is independently predicts cardiovascular malfunctioning and CRP is function as biomarker and a mediator of CHD [54]. Association between acute myocardial infarction (AMI) and high concentration of CRP in serum was first established by de Beer FC *et al.* [55]. After extensive clinical studies, CRP was emerging as independent predictor of cardiac malfunctioning and the concentration of serum CRP is directly correlated to AMI and cardiac death [56, 57]. Over few decades it was established that CRP along with lipid profiling (Cholesterol, LDL and HDL) can be a better predictor of the risk of CHD [58, 59].

Patients with high level of CRP from its baseline have high risk of development of myocardial infarction in future. Other inflammatory markers including SAA and IL-6 having similar correlation for AMI occurrence [57, 60]. Potential approach for the reduction of upcoming CHD in person with high CRP level could be usage of statin [61, 62] and aspirin [63]. Based on CRP functions including complement system activation, up-regulate of adhesion molecules production, triggering the production of nitric oxide, expression of nitric oxide synthase, CRP cut-points for clinical interpretation was established i.e. CRP concentrations <0.1 mg/dl are considered as low, 0.1–0.3 mg/dl considered as average, and > 0.3 mg/dl considered as high relative risk of CHD [64].

7.CRP IN CANCER

Evidences demonstrated that chronic inflammation plays an important role in carcinogenesis in human [65]. CRP, an inflammatory protein, elevate in circulation of cancer patients [66]. Various studies suggest that high concentration of CRP may not be associated with occurrence of cancer however it can increase the risk of carcinogenesis in healthy individual [67-69]. On the study on Danish population, Allin *et al.* demonstrated that if the CRP concentration of individual measured at baseline, it has 1.3 fold more risk of any cancer type [70]. Two fold risk of occurrence of lung cancer was observed in case of high CRP concentration as compared to low concentration of CRP from baseline [71].

A study on colorectal cancer demonstrated that elevated CRP may increase the risk of cancer up to 1.6 fold [68], however in contrast, no correlation of CRP concentration and occurrence of colorectal cancer was found [72, 73]. Likewise in breast cancer, association was not found between the disease pathogenicity and elevated concentration of CRP from the base level [74]. In case of prostate cancer, primarily the association of elevated level of CRP with disease pathogenicity was reported negative [73, 75]. So it was found that elevated CRP concentrate may increase the risk of any cancer type mainly lung and colorectal cancer.

8.CRP IN TUBERCULOSIS

From last century, incidence of tuberculosis (TB) has been dropped by the rate, approximately 1·5% per annum. Still TB remains the foremost infectious cause of mortality [76]. Approximate 23% of TB incidence is reported in India and out of which mortality rate is $1/4^{th}$. It was also reported that approximate 40% of Indian population have infection of TB however major proportion is latent TB. Recent trend indicated the reduction of TB burden in India however the rate is very slow. Because of geographical hindrance, numerous local cases are left behind the reported data might be because of high rates of recurrence of TB, delay in diagnosis, drug resistance, common symptoms with other disease, inadequate treatment etc. [77]. Xpert MTB/RIF (GXP), a nucleic acid amplification assay or more advance version Xpert MTB/RIF Ultra are common platform for the diagnosis of tuberculosis [78, 79]. However any version of GXP assay cannot be used to measure treatment response of TB.

Acid-fast bacilli (AFB) staining is an alternative to measure therapy response even in the frequent availability of GXP assay [80]. However, AFB staining is not suitable for the measurement of treatment response of patients who has shown sputum smear negative result [81]. The investigation of CRP level is commonly measured during pathogenicity of

active tuberculosis (TB) and it is frequently used in South Africa [82, 83]. Various study demonstrated that CRP has lower median in TB as compares to bacterial pneumonia [84]. In several study it was reported that CRP concentration was found at baseline after 2 month of anti TB therapy [85]. These studies suggested the prognostic use of CRP in tuberculosis.

9.CRP SOURCE

In inflammation, CRP is measured form serum of patients. So in inflammation condition, blood or other related tissue have elevated concentration of CRP [86, 87]. To make control and calibrator, active human CRP which is pentameric in nature; are purified from non-malignant ascites fluids (AF) and pleural effusion fluid (PF). CRP has calcium dependent affinity to phosphocholine and this feature is used to purify CRP form AF/PF [19]. In malignancy, inflammation would occur in initial or later stage. Independent study on lung, prostate, colorectal and ovarian cancer show association of CRP is disease pathogenicity [88, 89] and cancer fluid (CF) is also used for purification of pCRP to make control for immune assay. Monomeric form of CRP (mCRP) from active pentameric purified CRP (pCRP) can be developed with Urea chelation method [25].

Potempa *et al.* have expressed and purified cys- mutated recombinant mCRP (r_mCRP) form *E.coli* as host. Protein r_mCRP was expressed as inclusion bodies and solubilization was done using citraconyl anhydride [90]. Dortay *et. al.* expressed the CRP protein in different strains of *E.coli* including BL21 (DE3), BL21 (DE3) pLysS, BL21 (DE3) Codon Plus-RIL, BL21 Star (DE3) and Rosetta-gami cells however protein was not refolded properly. Further secretory expression of CRP was done in two eukaryotic hosts, namely the yeast *Kluyveromyces lactis* and the protozoon *Leishmania tarentolae*. They reported 2 mg/L of pCRP form *L. tarentolae* using phosphocholine column purification [91]. This yield is too low for commercializing of recombinant CRP for the preparation of control and calibrator. So for commercial feasibility, higher expression of recombinant active pCRP from yeast and mammalian system is recommended.

10.DISCUSSION AND CONCLUSIONS

CRP is an acute phase protein routinely used for the diagnosis of systemic inflammation. Two different conformational isoforms i.e. pentameric CRP (pCRP) and monomeric CRP (mCRP) have different functions. Mostly pCRP determination is used as an indicator of risk assessment of CVD. The elevated CRP concentration is associated with many malignancies primarily with colorectal cancer and lung cancer. Elevated level of CRP also found in non- malignant ascitic fluid and plural effusion. To make diagnostic platform, CRP is usually purified form ascitic fluid, plural fluid and cancer fluid. Recombinant CRP was expressed in various strain of *E.coli*, yeast *K. lactis* and the protozoon *L. tarentolae* however yield of purified CRP form *L. tarentolae* source is quite low for commercial viability. Current review suggests the routine diagnosis of CRP concentration for the monitoring of treatment response in various clinical conditions.

CONFLICTS OF INTEREST:

The authors declare that they have no conflicts of interest.

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