

Physiological Role of C - Reactive Protein as a Diagnostic Marker

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Abstract

C-reactive protein (CRP) is a long-established marker that belongs to a family of proteins known as pentraxin. The conserved nature of this protein among the evolution of vertebrate indicates this protein plays important roles during immunologic responses. In addition, it considered that CRP can act as a unique acute phase protein that having a direct activity on complementary system to removal of pathogens. The production of CRP in liver occurs mainly in responding to activation of interleukin- 6 (IL-6), and there is a good association has been found between the level of IL-6 and CRP. The normal human CRP concentration ranged 0.8 mg / L and is <10 mg / L in normal state, and concentrations larger than this value is consider as abnormal indicating an existence of infection. Also, many conditions can change the concentrations of CRP involved tissue necrosis, burns, trauma, surgery, inflammatory diseases that mediated immunologically, cancer and crystal-induced inflammatory diseases. There are 2 conformational isoforms of CRP including pentameric (pCRPs) and monomeric (mCRP) which having variable biological and antigenic electrophoretic properties. pCRP is a permanent form found in sera and is appeared as a very stable molecule, but the current evidences suggested that this form can be dissociated to mCRP in both *in vivo* and *in vitro*. The high expression of mCRP have demonstrated in diabetic plaque lesion concerning to the extensive systemic inflammations. Site for binding of CRP to phosphatidylcholine locates on lateral surface and requires binding for 2 Ca ions at a particular hydrophilic pockets called the Ca-dependent ligand binding. Recent reports have shown the ability of CRP to bind to LOX-1 receptor to induce the modification vascular responses to vasodilator, infiltration of leukocyte and activation of complement system.

Keywords: CRP, Pentraxin, Phosphatidylcholine, Ca-dependent ligand binding, Complement system,

1. Physiology of C-reactive protein

C-reactive protein (CRP) is a long-established marker, which identified in 1930 by Tillet and Francis in serum samples of patients with pneumonia, and is named due to its capacity (C) for precipitating the fractions of polysaccharides (PSs) from *Streptococcus pneumoniae*. However, this ability is rapidly disappearing as the patient cured and not detected in healthy individuals. Since this recognized as protein, the name become CRP (**Liu et al., 2014; Koenig, 2017; Swede and Braithwaite, 2017**). Acute phase is applied to classify the patients having serum samples positive to CRP, and many other acutely ill individuals have been described with acute phase (**Khanna et al., 2013; Chen et al., 2020**). The CRP is belong to a family of proteins known as pentraxin that named due to its ability for formation of a cyclic pentamer contains 5 similar non-glycosylated subunits, non-covalently bounds as well as organization in a very stable structure that resemble to discoid (**Ristagno et al., 2019; Baumert et al., 2021**). The weight of each monomer is 23027 DA and has a very resistant protein to lysis; whereas, the other members of this family are known as amyloid P components (**Cardoso and Leal, 2020**). The conserved nature of this protein among the evolution of vertebrate indicates this protein plays important roles during immunologic responses (**Macêdo Santiago et al., 2018**). In the presence of calcium (Ca), CRP binding to polysaccharides (PSs) of bacteria, fungi and parasites forming a complex that activates classical complement pathway (CCP) to promote for opsonization and phagocytic process (**LaFon et al., 2020; Williams et al., 2020**). In addition, it considered that CRP can act as a unique acute phase protein that having a direct activity on complementary system to removal of pathogens (**Pathak and Agrawal, 2019**). Through activation of neutrophils, CRP having the ability to stimulation cell-mediated cytotoxicity and promotes for degranulation of platelets with enhances the activity of Natural Killer cells (NKCs) (**Busch et al., 2020**). Under normal physiological status, CRP linked to ribonucleoproteins suggests that it acts directly in removing of necrotic tissues (**Fathi et al., 2018**).

Recently, many studies demonstrated that CRP could potentially play significant roles in elimination of bacteria. In one study in transgenic mice, it showed that the great level of human CRP produced in responding to endotoxin were act partially in protection from the lethal infections by *S. pneumonia* suggesting that this activity might be associated with the ability of CRP for binding to phosphocoline moieties found in G-PSs of *S. pneumonia* cell wall. Also, it observed that the transgenic mice were expressed an elevated level of resistance against the

lethal action of *Salmonella typhimurium* (Morrison et al., 2017). The normal human CRP concentration ranged 0.8 mg / l and is <10 mg / L in normal state. Concentrations larger than this value consider abnormal and indicate that there is an infection (Lee et al., 2017). The production of CRP in liver occurs mainly in responding to activation of interleukin- 6 (IL-6), and there is a good association has been found between the level of IL-6 and CRP (Figure 1) (Czajkowski, 2015; Foroughi et al., 2016).

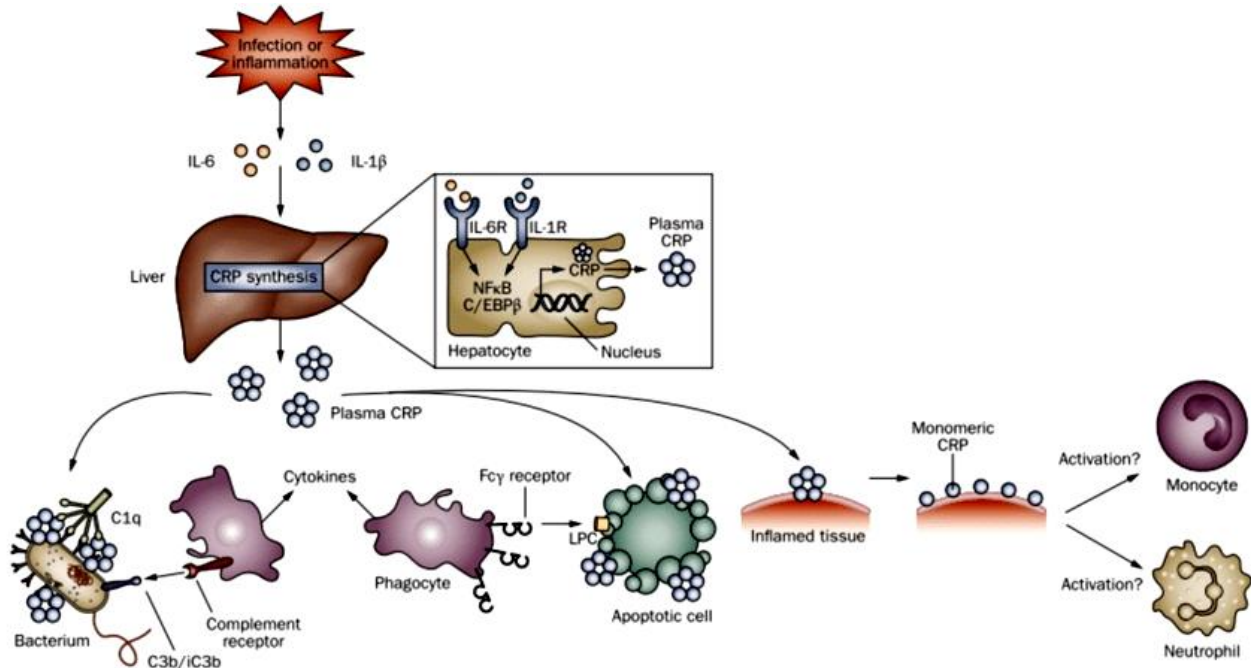


Figure (1): CRP synthesis, regulation and functions (Czajkowski, 2015)

Tumor necrosis factor-alpha (TNF- α) and IL-1 β are regulatory markers mediated in synthesizing of CRP that begun to secret throughout 4-6 hours post-stimulation and doubled at each 8 hours intervals to reach to the peak after 36-50 hours (Zhang et al., 2021). With continuous of intensive stimulation, the level of CRP increased greatly to reach more than 500 mg/L or even 1000 mg/L (Aray et al., 2016; Mac Giollabhuí et al., 2020). As the average half-life of CRP is 19 hours, it disappeared rapidly after stopping of stimulation (Yamamoto et al., 2021). If the main reason continues, CRP can be maintained for a long period; with the exception of extensive hepatic failure, in which, CRP increases continue because the existence of inflammatory processes, and the concentration of CRP still depending mainly upon the severity of stimulation and upon the rates of CRP synthesizing (Andrés et al., 2020). The level of CRP is independent

of the initial pathology and does not change by therapeutics or medical interventions (**Melnikov et al., 2020**). Nonetheless, CRP level could be modified when the inflammatory processes that cause acutely phase reactions are treated (**Del Giudice and Gangestad, 2018**).

The elevated concentration of the serum CRP can observe mostly in an invasive infection (**Paydar-Darian et al., 2019**). In fungal, bacterial and even immunodeficient patients, there is severe significant elevation in concentration of serum CRP. On the other hand, CRP concentration tends for reducing of almost viral diseases because uncomplicated influenza, mumps, measles and adenovirus can rarely cause elevated CRP concentrations (**Sigall Boneh et al., 2017; Tjendra et al., 2020**). Systemic Herpes simplex and Cytomegalovirus infections could induces an apparently alteration in concentrations of CRP (**Noronha et al., 2021**). In parasite infection, there are limited information about the behavior of CCP since some parasites as *Toxoplasma* and *Plasmodium* having the ability to causing a remarkable elevation in concentrations of CRP (**Miao et al., 2020**). In chronic diseases like leprosy and tuberculosis, abnormally moderate elevation in concentration of CPC was reported (**van Hooij et al., 2018**). In addition to infections, many conditions can change the concentrations of CRP involved tissue necrosis, burns, trauma, surgery, inflammatory diseases that mediated immunologically, cancer and crystal-induced inflammatory diseases (**Klein et al., 2020**). Other clinical cases like heat stroke, exercise and even some psychological diseases are related to some PCR changes. In the presence of serious illnesses, there is often a group of disease processes related to the expansion and / or loss of tissues related to normal or slightly high PCR (**Rasmussen et al., 2017; Naudé et al., 2018**). For unknown causes, there is a group of diseases, which unable to elevate CRP in acute phase responses, but when the patient responding to an illness, CRP will elevate, and can be followed for identification of disease or a condition that can flare-up of the underlying infection processes (**Lee et al., 2017; Giavri et al., 2021**).

2. CRP from pentameric to monomeric

It has been adopted that 2 conformational isoforms of CRP could be existed including pentameric (pCRPs) and monomeric (mCRP) which having variable biological and antigenic electrophoretic properties. pCRP is a permanent form found in sera and is appeared as a very stable molecule, but the current evidences were suggested that this form can be dissociated to mCRP in both *in vivo* and *in vitro* (**McFadyen et al., 2018; Yao et al., 2019**). There are 2 important mechanisms can be added to mCRP as following:

(1) *Local expression*: Many reports were detected the existence of mCRP in different extracted agencies involving inflammatory cells within plaques, smooth muscles and adipocytes (**Kochumon et al., 2019**). However, the mechanism of subunit synthesizing and its assembly to pCRP remains unknown (**Sproston and Ashworth, 2018**). Recently, *in vitro* reports have confirmed the local expressions and identification of mRNA in macrophage of plaque lesion (**Kaplan et al., 2018**). Additionally, highly expressions of the mCRP have demonstrated in diabetic plaque lesion concerning to the higher systemic inflammations (**Badimon et al., 2018**).

(2) *Local dissociation* of pCRP to mCRP was seen in membrane of apoptotic cell, and activates the platelet in plaque lesions to represent a great interface between atherogenesis, thrombosis as well as adaptive and innate immunity (**Ullah et al., 2020**). In cell membrane of activated platelet, phosphatidylcholine molecule appears with a great importance in this process, because phosphatidylcholine is capable to binding to circulated pCRP and induction its dissociation (**Tripathi et al., 2016**). In first step, hybrid intermediate molecules known as mCRPm are constituted to exhibit the CRP antigenicity to be retrain to native pCRP (**Mahmood, 2019**). Structure showing CRP antibody MCRPM that linked to increasing of assistance and mCRPm is quickly separated from the cell membranes and finally dissociated into mCRP that correlated to more powerful characteristics. However, mCRP is rarely existed in circulation through the commonly quantify techniques (**Li et al., 2018; Pathak et al., 2020**). The new technologies as RNA aptamers and employment of monoclonal antibody for mCRP were allowed to identification of nanomolar concentration of mCRP that represent a great importance method for additional understanding of mCRP effect in future studies (**Wang et al., 2017**).

3. Ligand and receptor

Phosphatidylcholine remains as one of the most importantly ligand of CRP in which, phospholipids undergoes an expression in apoptotic and necrotic eukaryotic cells, bacteria, fungi as well as in modified and native lipoprotein (**Al-Mekhlafi et al., 2021**). Site for binding of CRP to phosphatidylcholine locates on lateral surface and requires binding for 2 Ca ions at a particular hydrophilic pockets called the Ca-dependent ligand binding (**Williams et al., 2020**). Then, CRP is capable for interacting to other autologous ligands such as small ribonuclear protein, chromatin, histones, plasma lipoproteins and somatic membranes and cell walls of bacteria, fungi and parasites (**Pepys, 2018; Mouneshkumar et al., 2021**). Although, specific amino acids implicated in CRP ligands remains unknown, conformational modification of CRP can be

triggered due to exposure to acidic environment that at the inflammatory site to reveal in 2 additional binding sites in CRP (Bircheneder and Dresselhaus, 2016). Also, pCRP could be bound to CFHR4 protein and phosphocholine till be dissociated to mCRP (Pouw et al., 2018). Releasing of individual subunit can permit the exposing of hidden epitopes that having a different antigenically characteristics that having the ability for activation of complement system, lipoprotein, monocyte and platelets (Trofimenko, 2017). Concerning CRP receptors, IgG antibodies can recognize them in addition to Fc γ R that expressed by several cells such as myeloid and lymphoid lineages, leukocytes, platelet, mast cell and macrophage (Temming et al., 2021). Depending on the effect of the immunoglobulin receptor, the Fc γ R classified to high affinity CD64 as low affinity CD64, and to additionally a, b, and c subgroups Fc γ R by encoding genes (Yang et al., 2016). Mechanism of signal transduction to each receptor is depending upon inhibition motifs (ITIM) or activation motifs (ITAM), (Pang et al., 2017). Fc γ R is the only receptor that containing an ITIM that allowing for negative modulation of signal cascade (Coxon et al., 2017). The pCRP can be linked particularly to Fc γ RI and Fc γ RIIa in macrophages and platelet (Figure 1) (Moran, 2019); whereas, mCRP could linked to Fc γ RIII that expressed initially by endothelial cells and platelet (Seow, 2021).

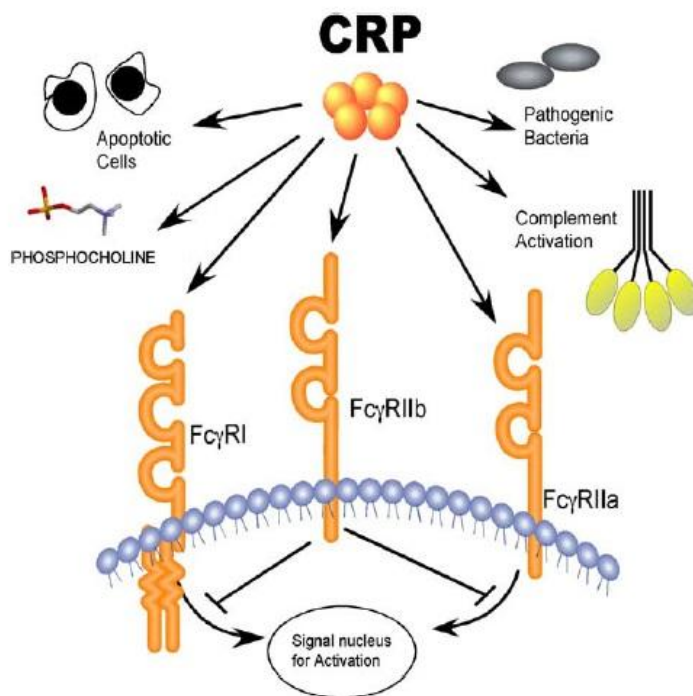


Figure (1): CRP ligands (Marnell et al., 2005)

Recent reports have shown the ability of CRP to bind to LOX-1 receptor to induce the modification vascular responses to vasodilator, infiltration of leukocyte and activation of complement system (**Akhmedov et al., 2022; Ghanbariha et al., 2022**). This link can share oxidized LDL and CRP pathways in endothelial dysfunctions and secretion of soluble LOX-1 in activated macrophage with those derived from mononuclear cell (**Ghazi-Khanloosani et al., 2019**). Based on these data, LOX-1 can possibly be used clinically as prognostic tool in acutely patients with coronary syndrome as well as in active pharmacological target due to decreasing of vascular toxicity as a result of linking of CRP to LOX-1 (**Marnell et al., 2005; Akhmedov et al., 2021**).

4. Pathophysiological roles

4.1. Atherosclerosis

Mechanisms for activation of inflammation could play important roles among different stages of atherosclerosis since early recruitment of leukocyte until the unstable plaque clearance (**Swastini et al., 2019**). Throughout many inflammatory biomarkers, CRP in most studies has confirmed an independent risk factor in cardiovascular disease, as it inhibits processes such as complement system activation, apoptosis, and apoptosis (**Boncler et al., 2019**). CRP having an intermediate effect as it associated with hardening of the arteries, formation of thrombosis, accumulation of lipid, recruitment of monocytes and activation of vascular cells (**Sandrini et al., 2020**). Two isotopes can involve at this process; pCRP that induces phosphatidylcholine-related inflammatory process on apoptotic cell surfaces and outside of LDL, and mCRP that allows platelets for regulation of platelet functions (**Philpot and Bhandari, 2019**).

4.2. Complementary system

This system includes a group of bioregulators and enzymes in addition to many biological markers that play important roles in acquired and innate immunities (**Figure 2**), (**Haapasalo and Meri, 2019**). True activation is necessary to defending against organisms with removing of necrotic and apoptotic cells (**Du et al., 2018**). However, extensive or insufficient activities may be contributed for pathogenic processes to a number of chronic infections like atherosclerosis (**Solomon et al., 2016**). Both isoforms of CRP; pCRP and mCRP, are having a capability for interacting to C1q, thereby activation of classical pathway (**Jia et al., 2021**). In recently carried out studies in atherosclerotic plaques, the findings were reported an elevation in concentration of

CRP, mRNA, C1q, C3, and C4 (Sproston and Ashworth, 2018; Sasaki et al., 2022), proposing that CRP might be involved in the classical pathway of memory complex formation aggressive (Tang et al., 2020; Sasaki et al., 2022). In addition, activation of this pathway increases the secretion and synthesizing of monocyte chemotactic protein (MCP-1) and IL-8, and stimulates a proliferation of arterial smooth muscle cells. These activities might be contributed for establishing and developing of atherosclerosis (Barre et al., 2018; Savaş et al., 2020). CRP is also involved in activating of nuclear factor kappa B (NF- κ B), a transcription factor existed in rapidly responding cell that is participated in responding to immunity and inflammation, cytokines, chemokines, molecules and growth promoters (Xu et al., 2019).

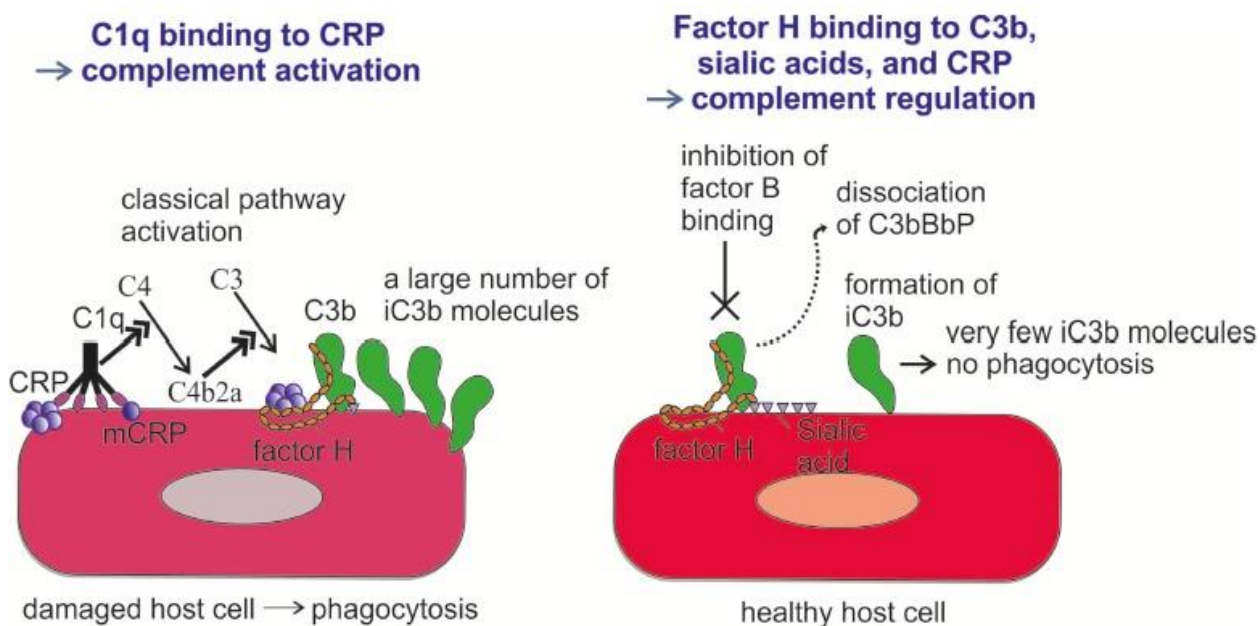


Figure (2): Regulation of the complement system by CRP (Haapasalo and Meri, 2019)

CRP also provides the binding sites for the mCRP isoform, which shows affinity for a member of factors H protein family that independently bind calcium (Józsi et al., 2019). In contrast, CFHR4 could be linked for pCRP throughout the Ca-dependent pathway (Sitepu and Harahap, 2020). This protein acts as a soluble negative regulator of the complement system by promoting for CRP recruiting to necrotic cell surfaces (Sproston and Ashworth, 2018). Excessive activity in this pathway increases circulating concentrations of C3a and C5a, potentially anaphylatoxin responding to local inflammation (Li et al., 2018). *In vitro*, information demonstrated that CR3

and CR5a could express to promote for attraction of monocyte, mast cell and lymphocyte chemotaxis and allowing for adhesion of endothelial molecules, response and production of IL- 1 and TNF in coronary atherosclerotic plaques (**Bhaskar et al., 2016**).

4.3. Interaction with cellular receptor

Family of Fc γ R contains a key that targets of CRP expression on many immune system cells that act as a regulatory factor for the processes of local inflammation like atherosclerotic plaque that regulate cytokine activation, proliferation, phagocytosis, degradation and secretion (**Newling et al., 2019**). Both pCRP and mCRP have the ability for binding with Fc γ RI, Fc γ RIIA, and Fc γ RIII, thereby enhancing structures that receiving cascades of intracellular signaling via ITAM (**Bircheneder and Dresselhaus, 2016**). Typically, these cataracts are caused by the progressive activation of the *Src* family of protein tyrosine kinases (PKTs), which phosphorylated residues of tyrosine in ITAM, and then, activating of KT's (**Xu et al., 2018**). These activities act for recruiting of several signaling molecules such as mitogen-activated protein kinase (MAPK), extracellular signal-controlled kinase (ERK), protein kinase C (PKC) and other kinases like hypoxides kinase (PI3K), intracellular adaptation molecules, and phospholipase C (PLC) in addition to other messengers like inositol 3-phosphate (PI3), diacylglycerol (DAG) and Ca (**Jamilian et al., 2017; Wang et al., 2019; Izquierdo et al., 2020**). Recently obtained evidences suggested that CRP initiates SHIP-1 phosphatase-activation in endothelial cells when it binds for Fc γ RIIb receptors that contains an intracellular ITIM-inhibitory region and is inactivated (**Dai et al., 2016; Coxon et al., 2017**).

4.4. Invasion, regulation and activation of immune cells

Recently studies have been suggested that PCRp directly regulate the activation of endothelial cells and dysfunctions through initiating an expression of intracellular hematopoietic proteins (MCPs), vascular E-selectin and intracellular adhesion molecules (**Bruserud et al., 2022**). In addition, CRP can induce the differentiation of human monocytes into the pro-inflammatory M1 phenotype and alter the cytokine secretion pattern of macrophages into the pro-inflammatory phenotype through Fc and NF-B receptor pathways (**Mirzavandi et al., 2020**). As well as, the *in vitro* information revealed that higher concentrations of CRP are associated with decreased synthesis of prostaglandin F1, a prostaglandin stabilizer involved in more importantly endothelial functions like cell proliferation of smooth muscles, platelet aggregation and vasodilation (**Fang**

et al., 2016). Also, CRP can act to overexpression of angiotensin receptor type 1 (ATR-1) by the NF- κ B and MAPK pathways to promote smooth muscle cell proliferation, remodeling, and migration from atherosclerotic lesions (**Jain et al., 2016**). Moreover, pCRP and mCRP can act significant differentiation activities through regulation the proliferation of endothelial progenitor cells (EPCs). Although pCRP promotes the proliferation of EPC with mainly induction the expression of non-inflammatory genes in these cells, mCRP induces the upregulation of pro-inflammatory genes in response without affecting the rate of EPC proliferation (**Ambasta et al., 2017; Pogue et al., 2017**). Finally, the downregulation of PCRP in mCRP could consider a "switch" to accumulation of inflammatory process associated with atherosclerotic plaques the formation (**Rocha et al., 2017; Melnikov et al., 2020**). Plaques could result in situ accumulation of mCRP, which promotes plaque growth through all the mechanisms described above (**Figure 2**) (**Enocsson et al., 2021**).

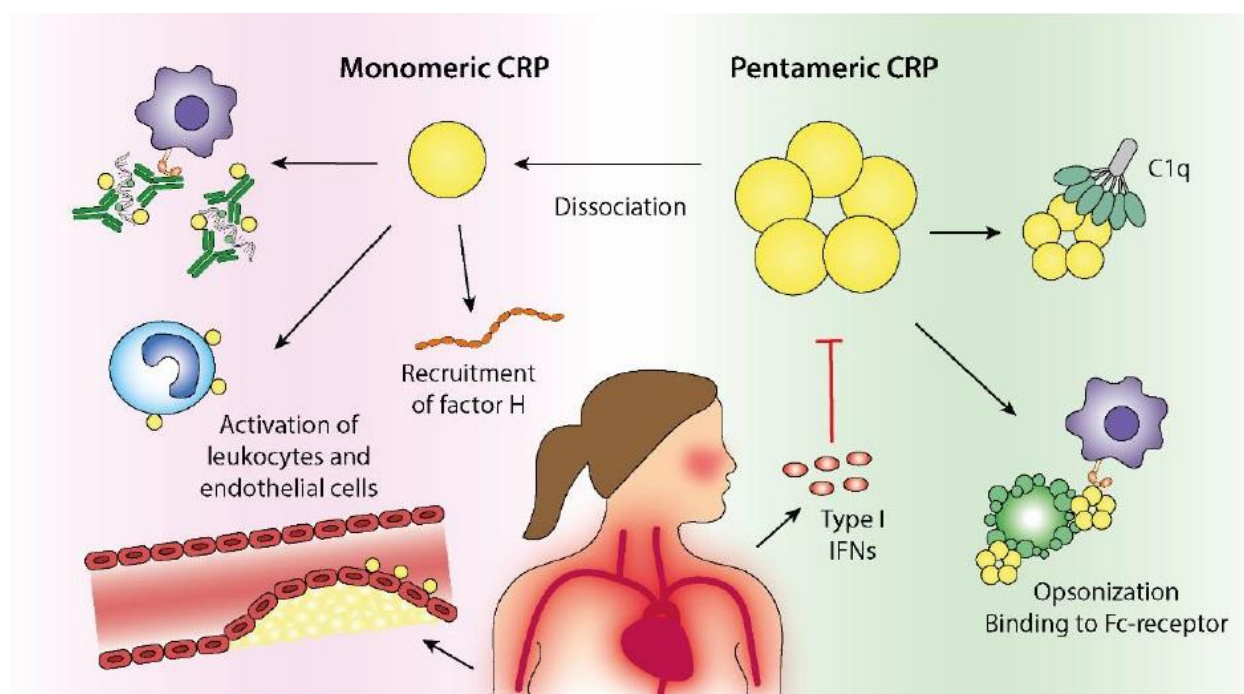


Figure (2): Immunoregulatory effects of pCRP and mCRP (Enocsson et al., 2021)

5. Evaluation of the C-reactive protein assay

5.1. Diagnosis of sepsis

Value of single CRP detection in the diagnosis was studied extensively in a variety of clinical conditions. In two recently published studies of critically ill patients, the best cross-sectional area

for sepsis detection was 50 mg/L. However, both studies depended on the daily measurement of CRP and comparisons were carried out sequentially using many methods. The most specific level of CRP has not yet been identified and may vary between different infections (**Pradhan et al., 2016; van Oers et al., 2020**).

5.2. The severity of the disease

The sole identification of CRP concentrations represents the rate of synthesis that depended upon intensity of inflammatory attacks (**Potempa et al., 2020**). Recently, many reports referred to that the concentrations of CRP in patients with sepsis can be categorized based on existence of ACCP/SCCM (**Tominaga et al., 2016; Wu et al., 2017; Ristovska et al., 2019**). However, average in patients with systemic inflammatory response syndrome (SIRS) can be classified as 70 mg/l, sepsis 98 mg/l, severe sepsis 145 mg/l and septic shock 173 mg/l, according to severity of inflammation (**Tessema et al., 2020**). It is reflected to varying degrees. Others have found similar results. In addition to its application in detection of sepsis level, CRP can be used as a prognostic indicator. The mean CRP concentration of the survivors was 70 mg/L, which was significantly greater than that of the survivors (18 mg/L) (**Zhao et al., 2020**). The increase in CRP during hospitalization was much greater in those who did not survive. Recently, the findings of researcher designated for assessment the outcomes by multiple markers of post-insertion inflammatory process, CRP act very well in the region under the 0.811 ROC curve (**Liu et al., 2020; Yang et al., 2022**).

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