C-reactive Protein and Malignancy: Clinico-pathological Association and Therapeutic Implication

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C-reactive protein (CRP) is a widely used systemic biomarker for diagnosing acute and chronic inflammation. During the past decade, serum CRP has been re-emphasized by extending its clinical use to the prediction or diagnosis of cardiovascular diseases and other conditions, particularly malignancies. 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. Preoperative CRP levels are parallel to the progression or pathological stages of malignancies, including gastric cancer in patients in our series. Elevated CRP is a determinant predictor of lower survival rates in patients with several cancers, including esophageal, colorectal, hepatocellular, pancreatic, urinary bladder, renal, ovarian and cervical cancer, after surgical resection. The measurement of serum CRP is simple, cheap, and available in daily practice. It can serve as an additional prognostic predictor for survival and post-treatment monitoring in cancer patients. In the future, CRP–lowering agents might offer a promising benefit in the prevention and therapy of many different types of cancer. (Chang Gung Med J 2009;32:471-82)

Key words: C-reactive protein, malignancy, inflammatory marker, gastric cancer

The linkage of inflammation and cancer was first reported by Rudolf Virchow in 1863, when he identified leucocyte infiltration in neoplastic tissues, and suggested that the sites of chronic inflammation were the origin of cancer. Since then, approximately 25% of all cancer patients are reported to have an association with chronic inflammation of either infectious or non-infectious causes. Examples of infectious causes of cancer are Helicobacter pylori (H. pylori) bacterial infection for gastric cancer, human papilloma virus (HPV) for cervical cancer, Epstein-Barr virus for nasopharyngeal cancer, and hepatitis B virus for hepatocellular carcinoma. Non-infection conditions include gastroesophageal reflux for Barrett’s esophagus, asbestos for bronchogenic cancer and mesothelioma, alcoholic cirrhosis for hepatocellular carcinoma, and inflammatory bowel diseases, including ulcerative colitis and Crohn’s dis-
ease, predisposing to colon cancers.

Serum C-reactive protein (CRP) is a very sensitive indicator of current disease activity for inflammation. It has been most widely used for the clinical diagnosis of acute or chronic inflammation. The introduction of a high sensitivity technique (hs CRP) enables identification of the group of patients with chronic inflammation that manifested by a minor elevation of CRP. We have measured preoperative serum CRP in 170 gastric cancer patients using a high sensitivity technique from 2000 through 2001 and studied the clinico-pathological correlation. Abnormally high levels (≥ 3.0 mg/L) of serum CRP were observed in 65 (38.2%) of our patients. Preoperative CRP was significantly associated with disease progression (tumor size, depth of wall invasion, lymph node metastasis, and distant metastasis) and pathological stages in our patients. In this article, after a long-term follow up study in our series, we intend to review reports in the literature about clinical usefulness of CRP for malignancies, and potential roles of CRP-lowering agents in cancer therapy.

Clinical use of C-reactive protein re-emphasized during this decade

CRP was first identified in the plasma of patients during the acute phase of pneumococcal pneumonia. It was named for its high binding affinity to the C-polysaccharide of Streptococcus pneumoniae. CRP was the first of the so-called acute phase proteins, which appeared in the serum of patients with infections or inflammation, during the acute and chronic stages. CRP is synthesized by hepatocytes as a part of the inflammatory response to tissue damage induced by infection, trauma, and malignant diseases. Thus, it is a sensitive but non-specific serum biomarker for inflammation and tissue damage.

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 plays an important role in the pathogenesis of atherosclerosis. The association between elevated CRP levels and future risk of major cardiovascular events has been recognized by some researchers in prospective studies. The introduction of a high sensitivity technique allows identification of a group of patients with minor elevations of CRP who are at higher risk of cardiovascular disease. Nearly two-thirds of the population has plasma CRP levels under 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. Chronic low-grade inflammatory conditions might be associated with these diseases.

CRP – the prototype of acute phase proteins

Acute phase proteins are a group of diverse proteins whose serum concentrations increase or decrease by at least 25% during the inflammatory states of the acute phase. CRP is the prototype of acute phase proteins. 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. They appear in the peripheral blood in response to infection, trauma, myocardial infarction, inflammatory disease (e.g. Crohn’s disease, rheumatoid arthritis) and malignancy. They are produced within a few hours by the liver in response to inflammatory cytokines such as interleukin (IL)-1, tumor necrotic factor (TNF)-α and in particular IL-6 (Fig. 1). Acute phase proteins were confirmed to be one of the major components of the serum biomarkers upregulated in patients with colon cancer using serum proteomic profiling with surface enhanced laser desorption ionization time-of-flight mass spectrometry (SELDI-TOF-MS) technology.

CRP – a classical member of pentraxin family

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. Based on the structural differences of subunit lengths, they were divided into two groups: short and long pentaxins. CRP and serum amyloid P-components (SAP) are the prototypes of short pentraxins and are produced from the liver in response
to IL-6.\textsuperscript{(14)} Pentraxin 3 (PTX3), a recently identified member, is a long pentraxin. PTX3 is rapidly produced from the cells involved in atherosclerotic lesions, namely vascular endothelial cells, vascular smooth muscle cells, macrophages, and neutrophils in response to inflammatory stimuli. CRP is produced by the liver and represents a systemic response to a local inflammation, whereas PTX3 is rapidly produced from damaged tissues and vascular beds in a local response to the inflammatory state of the vasculature. PTX3 is a superior vascular inflammatory biomarker for cardiovascular diseases.\textsuperscript{(14)} The association of PTX-3 with cancers was rarely reported until 2006, when overexpression of PTX3 was identified in soft tissue liposarcoma.\textsuperscript{(15)}

SAP is the serum precursor of the P component of amyloid. It probably serves as an opsonizing protein of the apoptotic cells by activating the complement system. Although also produced from the liver, SAP lacks the kinetics qualified for acute phase protein, when compared with CRP and PTX3.\textsuperscript{(16)} Unlike CRP and SAA, the association of SAP with the development or progression of cancer has rarely been reported.

**CRP and tumor microenvironment**

In tumor tissues, cancer cells are embedded in a microenvironment resembling chronic inflammation. In addition to tumor cells, the microenvironment contains leucocytes, lymphocytes and macrophages with cytokines and chemokines acting as mediators, reflecting a persistent inflammatory state (Fig. 1).\textsuperscript{(1)} This microenvironment may contribute to carcinogenesis through induction of genomic instability, epi...
Elevated CRP is most likely a response secondary to tumor necrosis, local tissue damage, and associated inflammation in patients with malignancies. CRP is produced in hepatocytes as a systemic response to cytokines in the blood stream, particularly IL-6, released from leukocytes within tumor microenvironment. 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. Thus, CRP is not only an epiphenomenon, or a response to tumor microenvironments, because it contributes to the disposing of tumor cells both dead and alive.

Regulation of CRP expression

The CRP gene is located on the short arm of chromosome 1 (1q21-q23). 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-1β. CRP synthesis requires transcriptional factors C/EBP family α/β/δ (CCAAT/enhancer binding protein), STAT3 (signal transducers and activators of transcription), and Rel (v-rel reticuloendotheliosis viral oncogene homolog-avian) protein following cytokine stimuli. They have binding sites in the promoter region of the CRP gene. The nuclear factor κB (NF-κB) subunits p50 and p65 through protein kinase C pathway is also involved in cytokine induction of CRP synthesis. The interactions of these transcription factors cause maximal induction of CRP expression in hepatocytes. Extrahepatic synthesis of CRP has also been reported in neurons, monocytes, lymphocytes and tumor cells as a local inflammatory response, but the amount is too little to influence serum CRP.
gastric cancer than in healthy control subjects in previous reports.\(^\text{4,36,57-60}\) Elevated CRP was significantly paralleled to progressive disease and advanced stage in those series as well as in ours (Fig. 2).\(^\text{4,36,57-60}\) However, long-term survival outcomes of gastric cancer patients with elevated CRP were not available in other series. Our 5-year survival rate of the group with high levels of CRP (\(\geq 3.0 \text{ mg/L; } n = 105\)) was significantly worse than that of patients with normal CRP levels (\(< 3.0 \text{ mg/L; } n = 65\)) (27.1% versus 54.1%; \(p = 0.0010\)) (Fig. 3). Our study clearly demonstrated that survival was significantly worse in patients with an elevated CRP compared with those with normal CRP levels.

Following potentially curative surgery, serum CRP usually decreases to normal levels in patients when the CRP levels were elevated before operation.\(^\text{23}\) Serum CRP may remain high for a prolonged period following a non-curative surgery, depending on the volume loading of residual tumor. Thus, CRP may be used postoperatively for the evaluation of treatment effectiveness or tumor recurrence after curative surgery. However, in the immediate postoperative period, CRP levels may vary depending on the degree of surgical stress caused by different operation procedures. For example, CRP levels were lower after laparoscopic approaches versus those after open procedures.\(^\text{61,62}\) Elevated CRP levels may also indicate the presence of surgical infections or complications. CRP levels were useful for the early prediction of post-surgical complications in patients with gastric cancer.\(^\text{63,64}\)

H. pylori infection is believed to play a causal role in the development of gastric cancers.\(^\text{65}\) It is blamed for the initiation of sequential histological changes in the gastric mucosa, from active gastritis, to atrophy, intestinal metaplasia, dysplasia, and finally to adenocarcinoma.\(^\text{65,66}\) H. pylori infection is often asymptomatic, but can also lead to the development of gastroduodenal ulceration and mucosa-associated lymphoid tissue lymphoma, the so-called Maltoma. The epidemiologic link between H. pylori and gastric cancer was first reported in 1991.\(^\text{67}\) The molecular mechanisms of the local immune response to H. pylori infection are complex. There is evidence that H. pylori infection induces the release of cytokines (IL-1\(\beta\), IL-2, IL-6, IL-8, IL-23 and IL-17 and TNF-\(\alpha\)) from both immune and non-immune cells.\(^\text{68,69}\) These cytokines enhance CRP production of hepatocytes in the infected patient, contributing to amplification of the ongoing inflammation. Through toll-like receptors, H. pylori infection also activates NF-kB and Mitogen-activated protein kinases (MAPKs) pathways to local COX-2 expressions in gastric epithelial cells to accelerate the inflammatory response.\(^\text{60}\)

Serum CRP is one of the inflammatory markers

![Fig. 2](image-url) Scatter plot of preoperative CRP level in 170 patients with gastric cancer according to the pathological stage (\(p < 0.001, \) \(p \) Stages I-II versus \(p \) Stages III-IV).

![Fig. 3](image-url) Kaplan-Meir survival curves of two groups of gastric cancer patients defined by serum CRP level cut-off value of 3 mg/L, as determined by the 95 percentile in 450 normal control subjects. The 5-year survival rate of elevated group \((n = 105)\) was significantly worse than that of the normal group \((n = 65; 27.1\% \text{ versus } 54.1\%; \log \text{ rank } p = 0.0010)\).
for H. pylori infection, but it is not a reliable or specific marker for the primary diagnosis or post-eradication follow-up of H. pylori infection.\cite{59,71} In patients with gastric cancer, serum CRP levels did not differ between the H. pylori-infected group and non-infected group.\cite{59} Precancerous lesions of the stomach may regress after successful H. pylori eradication.\cite{65,72} However, the benefits of H. pylori eradication for gastric cancer prevention is limited to patients who have not progressed into having mucosal atrophy or metaplasia.\cite{72}

Other serum inflammatory markers for malignancy

CRP and SAA are the two major acute phase proteins in humans. CRP and SAA are both suitable markers of acute phase responses, due to their rapid production and short half-life in circulation.\cite{73} Other systemic markers such as leukocyte count, erythrocyte sedimentation rate (ESR), or cytokine mediators lack the desirable characteristics of CRP and SAA.\cite{7,74}

Serum amyloid A (SAA)

SAA was first described in 1994 and is an apolipoprotein of very low density lipoprotein (VLDL and high-density lipoproteins (HDL). Like CRP, it is also synthesized in hepatocytes, immediately after induced by the proinflammatory cytokines IL-1, IL-6, and TNF-\( \alpha \) in response to inflammation. It may alter HDL metabolism during inflammation.\cite{73} Its sensitivity was comparable to that of CRP in tests for rheumatic and coronary artery diseases.\cite{75,76} SAA is not as widely used clinically as CRP. High SAA levels have been associated with malignancies, including gastric, lung, renal cell, colorectal, prostate, nasopharyngeal and breast cancers.\cite{77} High serum SAA levels have also been associated with aggressive diseases and poor survival outcomes.\cite{7,78}

Plasma cytokines

The measurement of plasma cytokines (interleukins, chemokines, etc) is difficult due to of their short plasma half-lives and the presence of blocking factors in the blood.\cite{7,79} Because most cytokines act locally, only the plasma cytokine levels of those (such as IL-6) entering the circulation with a systemic action are really meaningful. The association of plasma cytokines or chemokines with malignancy and their clinical significance are still under investigation.\cite{73} Among them, plasma IL-6 has been the most frequently studied.

**IL-6**

IL-6 is one of the most useful plasma cytokine markers in the acute phase response. It is a pleiotropic inflammatory cytokine that has a conflicting role in regards to tumor cells. It promotes the antitumor activity of macrophages to produce lymphokine-activated killer cells, and prevents apoptosis of neutrophils that aid in the killing of tumor cells. IL-6 stimulates CRP synthesis in the liver and indirectly helps the binding of CRP to tumor cells, leading to tumor cell lysis. Conversely, IL-6 favors tumor growth \textit{in vivo} of most cancers.\cite{80} IL-6 is also produced by tumor cells and platelets.\cite{81,82} It may stimulate tumor cell proliferation and induce leukocyte recruitment as part of an autocrine growth factor loop.\cite{83}

High serum IL-6 levels were detected in patients with breast, colorectal, gastric, pancreatic ovarian, lung, prostate and renal cell cancers, and in patients with melanoma, multiple myeloma, leukemia and lymphoma.\cite{80-83} High serum IL-6 levels have been associated with progressive diseases and poor survival.

**COX-2, a local inflammatory marker**

COX-2 is a local inflammatory marker. Unlike CRP, it is not a systemic marker. COX enzyme catalyzes the synthesis of prostaglandins from arachidonic acid. It has two isoforms: COX-1 and COX-2. COX-1 is constitutively expressed, and COX-2 is inducible and produces prostaglandins (PGE-2, etc) in response to various inflammatory stimuli (Fig. 1). COX-2 expression can be induced rapidly and transiently on exposure of cells to various external stimuli such as mitogens, inflammatory cytokines, growth factors, oncogenes, reactive oxygen species (ROS), ultraviolet irradiation, ionizing radiation, endotoxins, viral proteins, bacterial lipopolysaccharides (LPS), and phorbol esters.\cite{10}

COX-2 is highly expressed in patients with colon, stomach, breast, bladder, cervical, and skin cancer.\cite{84-86} COX-2 overexpression has been associated with uncontrolled cell proliferation and differentiation, inhibition of apoptosis, promotion of angi-
CRP and malignancy

...genesis and metastasis, and even resistance to radiation and chemotherapy.

Comparisons of CRP with other inflammatory markers such as serum IL-6, serum amyloid A and COX-2, have been reported regarding the survival or death of patients with infection, sepsis, cardiovascular diseases, or autoimmune diseases. These inflammatory markers were investigated independently by most researchers in patients with gastric cancer and other malignancies. No substantial superiority of CRP over other inflammatory markers has been confirmed for survival or risk factor of gastric cancer and other malignancies in reports in the literature. However, in a comparison study between COX-2 and CRP in patients with bladder cancers, only CRP was an independent prognostic factor in survival analysis. COX-2 is inferior to CRP for the prediction of survival. It was postulated that serum CRP can be measured with a greater accuracy and precision than COX-2.

Are CRP-lowering agents for cancer therapy as equally effective as they are for cardiovascular diseases?

CRP has been a promising therapeutic target for patients undergoing cardiovascular therapy. Among the drugs used in the treatment of cardiovascular diseases, COX inhibitors (aspirin, celecoxib etc), platelet aggregation inhibitors, lipid-lowering agents (statins), β-adrenoreceptor antagonists, antioxidants (vitamin E), and angiotensin converting enzyme inhibitors have been confirmed to be able to lower the serum CRP levels. Since elevated CRP levels have been demonstrated in patients with malignancies, CRP-lowering drugs should be theoretically effective in cancer prevention and therapy. Among them, only COX inhibitors and lipid-lowering agents (statins) have provided promising efficacy in cancer therapy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mostly widely prescribed of the COX inhibitors for patients with arthritis and cardiovascular disease. NSAIDs include aspirin and non-selective and selective COX inhibitors. COX-2 inhibitors may cause cell cycle arrest or apoptosis of abnormal cells and inhibit tumor growth through the inhibition of angiogenesis and neovascularization. They have been used to decrease the synthesis of prostaglandins, thus inhibiting tumor growth. Aspirin may influence intracellular signaling by inhibiting phospholipase activity. NSAIDs also effectively lower serum CRP in cancer patients. Researchers doing epidemiological studies have found an association between long term use of NSAIDs and a lower risk of colorectal, bladder, gastric, breast, lung, prostate, and ovary cancers. Experimental data also support the prophylactic effects of NSAIDs against the development of cancers. Many clinical trials of NSAIDs have shown promise in lowering the incidence of esophageal, gastric, prostate, ovarian, colorectal and breast cancers. A meta-analysis of nine published studies demonstrated that the use of aspirin or NSAIDs was associated with a reduced risk of gastric cancer in a dose-dependent manner. COX-2-selective inhibitors, as well as H. pylori eradication regimens, might be potentially effective in stopping the progression of gastritis to gastric cancer. H. pylori eradication may reduce the COX-2 expression in H. pylori gastritis until intestinal metaplasia has developed. However, before widespread use is recommended for chemoprevention, the benefits of NSAIDs must be weighed against their adverse effects, such as increasing risk of cardiovascular events.

Another CRP-lowering agent is statins (or HMG-CoA reductase inhibitors). Statins are used to lower cholesterol levels in people with cardiovascular disease or at risk of cardiovascular disease. In addition to their lipid lowering effect, statins are able to decrease serum CRP levels. Since elevated CRP levels have been demonstrated in patients with malignancies, CRP-lowering drugs should be theoretically effective in cancer prevention and therapy. Among them, only COX inhibitors and lipid-lowering agents (statins) have provided promising efficacy in cancer therapy.

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Other therapeutic attempts have been made to suppress CRP indirectly by targeting its inducing cytokines such as IL-6, IL-1, and TNF alpha for inflammation-associated diseases and cancers. Anti-IL-6 therapy has been tried with promising results in patients with multiple myelomas, and renal cell carcinomas. Anti-IL-6 monoclonal antibodies (mAb)
treatment could lower CRP levels below detectable limits in most patients. Anti-IL-6 mAb therapy may also improve cancer-related anorexia and cachexia in cancer patients as palliative treatment.80

**Perspectives**

The link of inflammation and cancer has been supposed since the report of Rudolf Virchow in 1863. Since serum CRP is a sensitive but nonspecific marker of inflammation, it might be helpful in the evaluation of malignant diseases. Preoperative CRP is closely associated with the progression and survival rate of patients with many types of malignancies. It may serve as an additional prognostic predictor for survival and post-treatment monitoring in cancer patients. Serum CRP measurements are simple, cheap, and available in daily practice. CRP-lowering agents may have promising roles for the prevention and therapy of malignancies in the future.

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C-反應性蛋白質和惡性腫瘤：
臨床病理的關聯和應用於治療的未來性

王嘉修 孫建峰

C-反應性蛋白質 (CRP) 是一種被廣泛而且長久使用的全身性生物標記，表示有急性或慢性
性的發炎。在過去十多年來 CRP 的角色再度被重視，其用途擴展至心血管疾病的預測和診
斷，並延伸至其他的問題如惡性腫瘤等。有一些前瞻性研究亦已發現 CRP 的升高對於未來
癌症的發生，具有高度的風險。有許多急性發的病人血清 CRP 發現有上升的現象。這都意
味著發炎和惡性腫之間有密切的聯結。當腫瘤的微環境釋出細胞因子，特別是白細胞介素
(IL)-6，會引發肝細胞製造 CRP。許多惡性腫瘤包括我們的腎癌系列，病人術前的 CRP 血清濃
度與腫瘤的進行程度或期別具有平行的關係。於食道、大腸直腸、肝細胞、胰臟、膀胱、腎
臟、卵巢和子宮頸癌手術切除後，CRP 值升高是不利於病人存活的重要預測因子。血清
CRP 是一種簡易、便宜，且一般醫療機構都能作的檢測。可提供癌症患者存活預測與治療後
追蹤監視參考。未來利用降低 CRP 的藥物作為癌症的預防和治療目的應該會有希望達成的。
(長庚醫誌2009;32:471-82)

關鍵詞：C-反應性蛋白質，良性腫瘤，發炎性分子生物標記，腎癌