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C-Reactive Protein Signaling Pathways in Tumor Progression

Eun-Sook Kim[1], Sun Young Kim[2] and Aree Moon[1,*]

[1]*Duksung Innovative Drug Center, College of Pharmacy, Duksung Women's University, Seoul 01369,*
[2]*Department of Chemistry, College of Science and Technology, Duksung Women's University, Seoul 01369, Republic of Korea*

Abstract

Many cancers arise from sites of chronic inflammation, which creates an inflammatory microenvironment surrounding the tumor. Inflammatory substances secreted by cells in the inflammatory environment can induce the proliferation and survival of cancer cells, thereby promoting cancer metastasis and angiogenesis. Therefore, it is important to identify the role of inflammatory factors in cancer progression. This review summarizes the signaling pathways and roles of C-reactive protein (CRP) in various cancer types, including breast, liver, renal, and pancreatic cancer, and the tumor microenvironment. Mounting evidence suggests the role of CRP in breast cancer, particularly in triple-negative breast cancer (TNBC), which is typically associated with a worse prognosis. Increased CRP in the inflammatory environment contributes to enhanced invasiveness and tumor formation in TNBC cells. CRP promotes endothelial cell formation and angiogenesis and contributes to the initiation and progression of atherosclerosis. In pancreatic and kidney cancers, CRP contributes to tumor progression. In liver cancer, CRP regulates inflammatory responses and lipid metabolism. CRP modulates the activity of various signaling molecules in macrophages and monocytes present in the tumor microenvironment, contributing to tumor development, the immune response, and inflammation. In the present review, we overviewed the role of CRP signaling pathways and the association between inflammation and cancer in various types of cancer. Identifying the interactions between CRP signaling pathways and other inflammatory mediators in cancer progression is crucial for understanding the complex relationship between inflammation and cancer.

Key Words: C-reactive protein, Inflammation, Tumor progression

INTRODUCTION

Despite the various strategies for treating cancer, cancer-related mortality remains a major cause of death worldwide (Bray *et al*., 2018). Localized increases in immune cell infiltration and the systemic inflammatory response to tumors can be important indicators of cancer progression and prognosis (Coussens and Werb, 2002; Hanahan and Weinberg, 2011; Dolan *et al*., 2017). Inflammation in the tumor microenvironment has been associated with the promotion of tumor growth, invasion, and metastasis, making inflamed cancers more aggressive and prone to metastasis (Hanahan and Weinberg, 2011). Chronic inflammation creates a local microenvironment that can facilitate tumor progression through interactions between tumor cells, immune cells, and stromal cells (Gómez-Valenzuela *et al*., 2021). The local microenvironment formed by chronic inflammation affects cellular plasticity through complex regulatory cascades involving the tumor and stromal cells (Varga and Greten, 2017). At least 20% of all cancers are initiated by chronic inflammatory conditions, and inflammation induced by the tumor itself is highly associated with most solid malignant tumors (Grivennikov *et al*., 2010; Siegel *et al*., 2016).

Cytokines play a role in alerting immune cells to the presence of infections and tissue damage. However, persistent cytokine production at a specific site can stimulate immune cells to secrete more cytokines, leading to a chronic inflammatory state that promotes cancer growth (Greten and Grivennikov, 2019). The inflammatory cytokines associated with carcinogenesis include interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α), which can stimulate or inhibit tumor growth and progression (Dranoff, 2004).

C-reactive protein (CRP), an inflammatory biomarker, is an acute-phase protein primarily synthesized in the liver in response to various inflammatory stimuli (Volanakis, 2001). CRP is composed of five identical subunits forming a planar ring that gives high stability to the protein. It can bind to various endogenous and exogenous ligands exposed on dam-

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***Corresponding Author**
E-mail: armoon@duksung.ac.kr
Tel: +82-2-901-8394, Fax: +82-2-901-8386

aged, necrotic, and apoptotic cell membranes. Through this binding, CRP strongly activates the classical complement pathway, which can exacerbate tissue damage and potentially lead to more severe diseases (Pepys and Hirschfield, 2003). CRP levels are increased in response to infections and tissue damage, as well as in various active disease states. Elevated CRP levels have been found to be associated with several cancers, including breast, lung, gastric, and colorectal cancer, hepatocellular carcinoma, and renal carcinoma (Roxburgh and McMillan, 2010; Wu *et al*., 2011). Serum CRP levels have been associated with tumor size, clinical pathological characteristics, and lymph node metastasis (Lee *et al*., 2009; Wang and Sun, 2009). CRP is also considered an important biomarker for tumor prognosis and treatment responses (Kishi *et al*., 2015; Shrotriya *et al*., 2015; Tang *et al*., 2015; Frydenberg *et al*., 2016; Shibutani *et al*., 2016).

This review summarizes the role of CRP signaling in cancer progression and the interaction between inflammation and cancer in the tumor microenvironment (Fig. 1). Increased CRP levels in the inflammatory and tumor microenvironment contributes to the promotion of various cancers, including breast, liver, renal, and pancreatic cancer, through interactions with various inflammatory molecules. CRP also induces angiogenesis and increases the secretion of inflammatory factors in the tumor microenvironment. In conclusion, this review provides insights into the signaling and role of CRP as an inflammatory marker in tumorigenesis, offering potential therapeutic strategies targeting this pathway.

BREAST CANCER

Breast cancer is one of the most prevalent malignancies among women (Jemal *et al*., 2007). Triple-negative breast cancer (TNBC) has been associated with high recurrence rates and poor survival in breast cancer patients (Pierce *et al*., 2009; Metzger-Filho *et al*., 2012). Cancer metastasis is a major cause of death in breast cancer patients (Chambers *et al*., 2002). Many types of cancer originate from the sites of chronic inflammation, which causes an inflammatory microenvironment around the cancer (Balkwill and Mantovani, 2001). Chronic inflammatory conditions promote the development of cancer in various organs, including the breast, stomach, colon, and liver (Ames *et al*., 1995; Platz and De Marzo, 2004; Hojilla *et al*., 2008).

The molecular mechanisms underlying CRP increases in an inflammatory environment have been previously reported in breast epithelial cells (Kim *et al*., 2014). The treatment of MC-

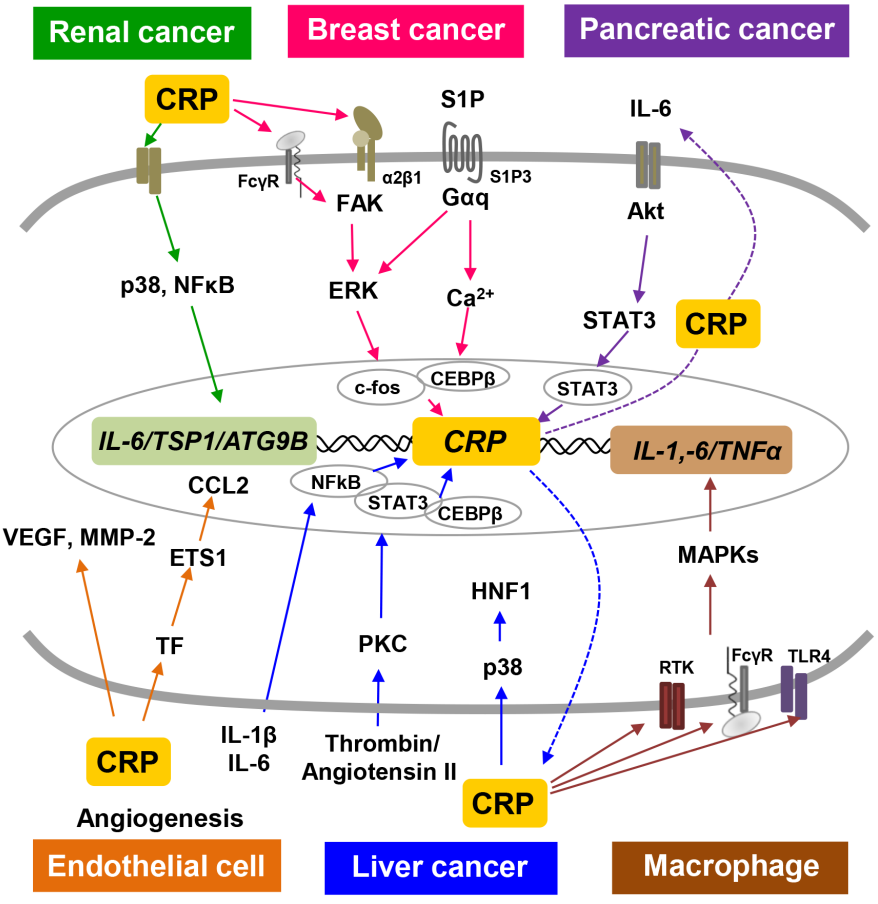

Fig. 1. CRP signaling pathways in various cancers and angiogenesis. The six different colored-arrows show the representative CRP signaling pathways occurring in each cancer. Renal cancer: Green, Breast cancer: Pink, Pancreatic cancer: Purple, Endothelial cell: Orange, Liver cancer: Blue, Macrophage: Brown.

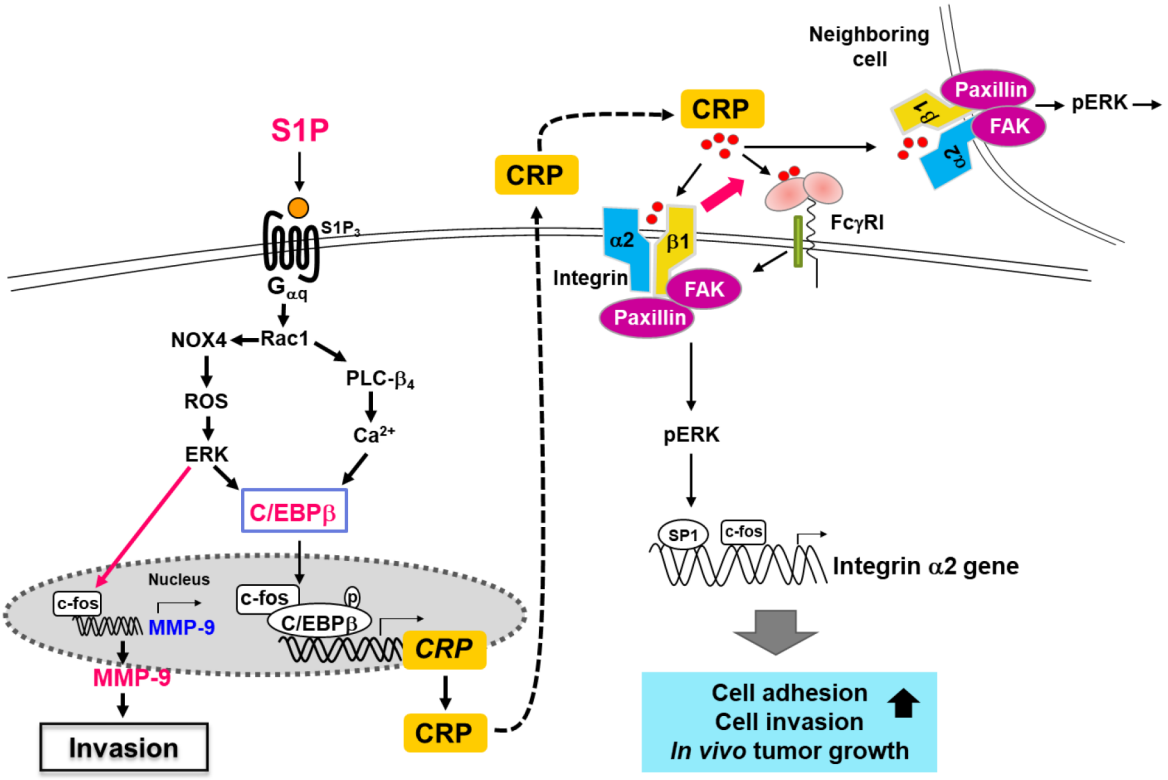

Fig. 2. The CRP signaling pathways involved in breast cancer progression (Modified from Kim *et al.*, 2014, 2018).

F10A breast epithelial cells with the inflammatory lipid sphingosine-1-phosphate increased the expression of CRP, which was subsequently secreted into the extracellular space. The secreted CRP stimulated MCF10A cells again through receptors, increasing the expression of integrin α2. The increased expression of integrin α2 by CRP involved the transcription factors c-fos and specificity protein 1 (SP1). Additionally, the binding of integrin α2 and CRP induced the activation of focal adhesion kinase (FAK), paxillin, and extracellular signal-regulated kinase (ERK), resulting in the upregulation of matrix metalloproteinases (MMP)-9 and the induction of adhesive and invasive phenotypes (Kim *et al.*, 2014, 2018). Thus, the molecular connection between S1P and CRP plays a significant role in increasing the invasive phenotype and promoting tumor formation in TNBC cells (Fig. 2).

CRP is highly expressed and secreted in highly invasive MDA-MB-231 TNBC cells, highlighting the significance of endogenous CRP in MDA-MB-231 TNBC cells. The knockdown of CRP reduced proliferation, invasion, and tumor formation in MDA-MB-231 TNBC cells. *In vivo* studies using chick chorioallantoic membrane (CAM) analysis and xenograft mouse models suggested that CRP is involved in angiogenesis and tumor growth in TNBC cells (Kim *et al.*, 2018). Elevated serum CRP levels are closely related to breast cancer invasion, metastasis and poor prognosis (Ravishankaran and Karunanithi, 2011). A significant association between high CRP levels and TNBC and luminal B breast cancer in premenopausal women has been reported (Agresti *et al.*, 2016). In contrast, another study found an association only with hormone receptor-positive and HER2-negative breast cancer (Hong *et al.*, 2013). The expression levels of CRP were correlated with vascular endothelial growth factor (VEGF) expression, Ki-67 labeling index, and body mass index (BMI) values. Highly proliferative tumors, including TNBC, showed enhanced neovascularization. In breast cancer, the expression levels of VEGF were reported to be associated with poor recurrence-free survival (RFS) (Toi *et al.*, 1995). Additionally, Ki-67 labeling index values were related to overall survival (OS) in breast cancer (Elston and Ellis, 1991). Increased breast cancer risk is associated with weight gain and obesity in women, especially in postmenopausal patients, and there is a significant correlation between CRP expression levels and BMI values (Dossus *et al.*, 2014).

Obesity is a well-established risk factor for postmenopausal breast cancer (Calle and Kaaks, 2004). Crown-like structures (CLS) are frequently found in the breasts of obese women, and the extent of CLS is correlated with adipocyte size, reflecting the severity of peritumoral inflammation in the breast (Subbaramaiah *et al.*, 2012). The increased secretion of CRP in obese states may be involved in the development and progression of breast cancer, although the molecular mechanisms are only partially understood. Specifically, in the inflamed breast tissue of obese women, levels of the enzyme cyclooxygenase-2 (COX-2), which is involved in inflammation and prostaglandin synthesis, are increased. This directly contributes to the increased activity of aromatase, playing a significant role in breast cancer development and stimulating the proliferation of tumorigenic breast epithelium (Subbaramaiah *et al.*, 2012). The inhibition of COX-2 resulted in reduced CRP levels, indicating a potential connection between inflammation and es-

trogen production in the context of breast tumor development (Bogaty *et al*., 2004). This suggests that obesity-related aromatase activity is associated with inflammation in breast tumor formation. Besides its local regulation of estrogen synthesis in breast tissue, CRP can also systemically increase circulating estrogen levels in obese women.

Recently, significant CRP levels were detected in nipple aspirate fluid (NAF) collected from women with benign breast diseases. This suggests that increased levels of CRP in breast secretions may serve as an early and non-invasive biomarker for inflammation and a pre-cancerous breast microenvironment (Lithgow *et al*., 2006). Cancer NAF from postmenopausal women contains higher levels of CRP compared to premenopausal cancer (Mannello *et al*., 2010). This suggests a potential role of CRP accumulation in the breast microenvironment during the progression of breast cancer.

PANCREATIC CANCER

Pancreatic neuroendocrine neoplasms (pNENs) are known as the most aggressive neuroendocrine malignancies, and their incidence is increasing annually (Dasari *et al*., 2017; Daskalakis, 2021). The prognosis of pancreatic cancer has remained largely unchanged over the past 20 years, with an overall 5-year survival rate of only 10% (Siegel *et al*., 2019; Sun *et al*., 2020). Despite advancements in diagnostic technologies, the diagnosis of pancreatic cancer is often delayed due to the absence of early symptoms. Preoperative elevations in CRP levels were shown to impact the poor prognosis of pNEN patients (Wiese *et al*., 2016). CRP is primarily synthesized in the liver and is a protein that is rarely produced in atherosclerotic lesions, kidneys, neurons, or pulmonary mast cells (Dong and Wright, 1996; Yasojima *et al*., 2001). The synthesis of CRP is mainly increased by IL-6, which is secreted by macrophages and T cells (Weinhold and Ruther, 1997). All inflammatory processes have the potential to activate IL-6, leading to an increase in CRP concentrations in the systemic circulation (Pepys and Hirschfield, 2003).

The IL-6 stimulation of pancreatic neuroendocrine tumor cells (BON1 and QGP1) leads to the upregulation and secretion of CRP. IL-6 was also secreted by CRP-stimulated BON1 cells, and both CRP and IL-6 increased the invasion of BON1 and QGP1 cells (Schimmack *et al*., 2019). ERK, AKT, and/or signal transducer and activator of transcription 3 (STAT) signaling pathways are important effector pathways strongly associated with the intrinsic malignant characteristics of cancer cells. The phosphorylation of ERK/AKT/STAT3, along with increased CRP and IL-6 expression, was observed in tissues from pNEN patients with increased CRP serum levels (Schimmack *et al*, 2019). In summary, CRP was internalized through receptor binding or endocytosis in BON1 and QGP1 cells, triggering IL-6 production and activating the IL-6/AKT/STAT3-CRP axis. The cross-stimulation between CRP and IL-6 in these cells may represent a positive feedback mechanism that promotes tumor progression (Schimmack *et al*, 2019). STAT3 is a protein that plays a pivotal role in the response to inflammatory mediators. It is involved in regulating cell growth, survival, and differentiation and acts as a significant regulator of the expression of the IL-6 gene (Levy and Darnell, 2002; Yu *et al*., 2009). Both CRP and STAT3 are potential components of the connection between inflammation and cancer (Mantovani *et al*., 2008). Elevated CRP and tumor markers levels were both associated with poor prognostic indicators in patients with resected pancreatic ductal adenocarcinoma.

LIVER CANCER

Liver cancer is one of the most common cancers worldwide and the third cause of cancer-related mortality (Sung *et al*., 2021). Chronic hepatitis B and hepatitis C infections are the main causes of liver cancer. Chronic inflammation is considered a key mediator of liver cancer, leading to fibrosis, cirrhosis, and eventually, liver cancer (Cervello and Montalto, 2006; Nikolaou *et al*., 2013).

CRP is produced by the liver. Thus, it can potentially be influenced by chronic liver diseases. In recent studies, elevated levels of CRP were associated with the poor prognosis of patients with liver cancer (Hashimoto *et al*., 2005; Sieghart *et al*., 2013). High CRP levels were observed in patients with liver failure (Park *et al*., 2005) and were associated with poor outcomes in patients with liver cirrhosis (Blot *et al*., 1993). Studies in hepatocellular carcinoma cell lines found that CRP synthesis was mainly stimulated by cytokines, particularly IL-1β and IL-6 (Majello *et al*., 1990; Toniatti *et al*., 1990; Kleemann *et al*., 2003). Transcription factors involved in IL-6-mediated CRP synthesis include STAT3 and CCAAT/enhancer-binding protein (C/EBP) family, especially C/EBPα, β, and δ. NF-κB subunits p50 and p65 are also involved in cytokine-induced CRP synthesis. Thrombin, IL-8, and angiotensin II could be potential candidates to mediate CRP induction within the body via protein kinase C (PKC). Their receptors are present on hepatocytes, and they are produced during sepsis and inflammatory conditions concurrently with elevated CRP plasma levels (Maekawa and Tollefsen, 1996; Wigmore *et al*., 1997). The activation of PKC is known to result in the phosphorylation of Ser 105 within the activation domain of C/EBPβ, enhancing its transcriptional activity (Ghosh and Karin, 2002; Su *et al*., 2002; Moscat *et al*., 2003). Therefore, these findings demonstrate the relevance of the PKC pathway in CRP gene expression in liver cancer.

Ruxolitinib, a Janus kinase (JAK) inhibitor, was found to completely inhibit the secretion and mRNA expression of CRP induced by lipopolysaccharide (LPS) in primary human hepatocytes and human hepatoma HepaRG cells. Similarly, it suppressed the upregulation of CRP induced by various Toll-like receptor agonists, as well as pro-inflammatory cytokines IL-1β, IL-6, and TNFα, and neutralized the LPS-mediated induction of serum amyloid A, fibrinogen, haptoglobin, and serpin. Ruxolitinib also blocked the activation of the IL-6/JAK/STAT pathway induced by LPS (Febvre-James *et al*., 2020). These results indicate that ruxolitinib could target the IL-6/JAK/STAT signaling cascade in inflammatory human liver cells, thereby inhibiting CRP induction and highlighting the potential of ruxolitinib as a promising therapeutic agent for modulating inflammatory responses in liver cells and associated conditions.

Coronary artery disease (CAD) is a substantial global health concern and a major contributor to atherosclerosis (Hansson, 2005). Proprotein convertase subtilisin kexin 9 (PCSK9), a significant regulator of low-density lipoprotein (LDL) metabolism, plays a crucial role in lipid and cardiovascular health, primarily expressed in liver cells (Abifadel *et al*., 2003). Elevated plasma CRP concentrations have been positively correlated

with an increased risk of cardiovascular diseases, including dyslipidemia. According to research conducted by Cui *et al*. (2016), CRP could activates the p38MAPK pathway, leading to increased expression of nuclear HNF1α in HepG2 cells, thereby contributing to the upregulation of PCSK9. A previous study reported that PCSK9, as a secreted factor, played a crucial role in promoting the degradation of LDL receptors (LDLRs), reducing the membrane recycling of LDLR, and consequently impeding the uptake of LDL particles. These results demonstrate the association between CRP, PCSK9, and LDL uptake in HepG2 cells.

RENAL CANCER

Renal cell carcinoma (RCC) is the most common solid lesion within the kidneys (Ozturk, 2015), comprising 2-3% of adult malignancies (Flum *et al*., 2016) and accounting for 85% of primary renal tumors (Bokhari and Tiscornia-Wasserman, 2017). It commonly metastasizes to the lungs, liver, bones, brain, adrenal glands, and lymph nodes, but rarely spreads to the skin, thyroid, or pancreas (Wolf *et al*., 2015). Clear cell renal cell carcinoma (CCRCC), a subtype of RCC, makes up approximately 75% of all RCC cases (Feng *et al*., 2016). Recent studies found that CRP expression was significantly associated with OS time in RCC patients (Fujita *et al*., 2016; Dalpiaz *et al*., 2017; Guo *et al*., 2017).

Autophagy related 9B (ATG9B) is involved in the autophagic process of delivering cellular components degraded by autophagosomes to lysosomes for digestion (Zavodszky *et al*., 2013), a common occurrence in the carcinogenesis process. The expression of CRP in CCRCC cells was reported to be positively associated with ATG9B expression. The inhibition of CRP expression resulted in a decrease in ATG9B expression, while overexpression led to an increase in ATG9B expression. Serum CRP protein levels were significantly higher in CCRCC patients compared to normal patients. In summary, the expression levels of CRP and ATG9B in CCRCC showed a positive correlation, indicating poor CCRCC status (Ma *et al*., 2017). These findings suggest that the abnormal overexpression of CRP and ATG9B may play a role in promoting CCRCC development.

CRP is significantly increased in patients with diabetic nephropathy. A study by Wang *et al*. (2012) suggested that CRP directly exerted pro-inflammatory effects on human renal tubular epithelial cells (HK-2 cells). CRP induced the release and mRNA expression of IL-6 and TSP-1 proteins from HK-2 cells by activating the p38MAPK and NF-κB signaling pathways. It also increased the expression of TGF-β1, indicating the significant role of CRP in propagating and prolonging inflammation in renal fibrosis (Baer *et al*., 2006).

ANGIOGENESIS

Tumor cells can infiltrate blood or lymphatic vessels, circulate within the vasculature, and then metastasize to other sites where they can proliferate (Folkman, 1971). Growth of the vascular network is crucial for the dissemination of cancer cells in metastatic spread within cancer tissues. CRP is known as a potent activator of angiogenesis and is associated with the formation of immature microvessels in the body (Slevin *et al*., 2010). CRP dissociated into monomeric CRP (mCRP) at the endothelial cell membrane, and mCRP increased tissue factor (TF) expression and induced angiogenic effects by activating the F3-TF-ETS1-CCL2 axis (Peña *et al*., 2016). Additionally, mCRP upregulated the endothelial expression of CD32 and CD64 (Devaraj *et al*., 2005), promoting migration, wound repair, and tubular formation. mCRP has also been demonstrated to promote angiogenesis by increasing vascular proliferation, migration, and tube-like structure formation *in vitro*, as well as stimulating blood vessel formation *in vivo*, according to the chorioallantoic membrane assay. mCRP induced the expression of several key molecules involved in angiogenesis, including VEGFR2/KDR, platelet-derived growth factor (PDGF-BB), inhibitor of DNA binding/differentiation-1 (ID-1), and notch family transcription factors (Notch1 and Notch3). Additionally, mCRP promoted the stabilization and maturation of cysteine-rich angiogenic inducer 61 (CYR61/CCN1), a molecule rich in cysteine that induces angiogenesis (Turu *et al*., 2008). These actions play a central role in the main stages of blood vessel formation and remodeling. mCRP induced the expression of Notch3 and N-cadherin while down-regulating VE-cadherin. mCRP and Notch3 acted cooperatively in endothelial cells, increasing endothelial cell proliferation, migration, and tube formation, thereby playing a role in vascular development, remodeling, and maturation. Additionally, mCRP stabilized vascular structures by regulating of VE-cadherin and N-cadherin expression (Boras *et al*., 2014).

CRP was demonstrated to upregulate the expression of VEGF-A in various cell types, including bovine aortic endothelial cells, human coronary artery endothelial cells, and monocytes (Bello *et al*., 2008; Turu *et al*., 2008). CRP was shown to activate the expression of hypoxia-inducible factor (HIF)-1α and MMP-2, as well as upregulate the expression of VEGF in adipose-derived stem cells. These effects lead to increased endothelial tube formation and vascular proliferation (Chen *et al*., 2016). CRP was found to promote angiogenesis by specifically enhancing the formation of newly developed microvessels around atherosclerotic plaques and in the ischemic penumbra following acute ischemic stroke (Krupinski *et al*., 2006; Slevin *et al*., 2010). CRP was also shown to induce inflammation and increase the permeability of abnormally developing microvessels after tissue damage (Slevin *et al*., 2015). These effects could contribute to an increased risk of dementia.

TUMOR MICROENVIRONMENT: MONOCYTES AND MACROPHAGES

Monocytes and macrophages, types of white blood cells, are both integral components of the immune system (Akiyama *et al*., 1988). Monocytes primarily function as circulating immune cells involved in immune surveillance and inflammatory responses. However, upon migration to tissues and differentiation into macrophages, their functions become more specialized. Macrophages possess a diverse range of functions critical to immune defense and tissue homeostasis. These functions include phagocytosis, which involves the engulfment and clearance of pathogens and cellular debris, as well as antigen presentation to activate immune responses. Macrophages also secrete cytokines, participate in tissue remodeling, and modulate immune responses (Schenten and Medzhitov, 2011). Importantly, the roles of monocytes and

macrophages extend to cancer development and progression, with their functions within the tumor microenvironment exhibiting both pro-tumor and anti-tumor effects. Understanding the dynamic interplay between monocytes, macrophages, and the tumor microenvironment is crucial for comprehending the complexities of cancer biology and devising effective therapeutic strategies.

CRP can affect various signaling molecules in macrophages and monocytes, leading to diverse influences on their behavior and function. TLRs recognize pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), thereby inducing innate immune responses (Tang *et al*., 2012). CRP was found to interact with TLR4, resulting in the activation of downstream signaling pathways (McCarthy *et al*., 2014). This interaction between CRP and TLR4 can lead to the promotion of pro-inflammatory cytokine production, including TNF-α and IL-6, in macrophages and monocytes. CRP can interact with cell surface receptors on macrophages and monocytes, such as Fc gamma receptors (FcγRs), complement receptors, including C1q, and TLRs. The binding of CRP to these receptors initiates intracellular signaling cascades, including mitogen-activated protein kinase (MAPK) activation. CRP can activate receptor tyrosine kinases (RTKs), such as the epidermal growth factor receptor (EGFR), or directly activate protein kinases involved in MAPK signaling. According to research conducted by Den Dunnen and colleagues, CRP has the ability to bind to phosphatidylcholine (PC) found on damaged or dying cell membranes (Newling *et al*., 2019). This interaction between CRP and PC, in conjunction with TLR signaling, promotes the production of cytokines, specifically TNF, IL-1β, and IL-23. Furthermore, the PC:CRP complex contributes to glycolytic reprogramming and fatty acid synthesis induced by the FcγRI and FcγRIIa signaling pathways, involving FcγRI/FcγRIIa-Syk-PI3K-AKT2 (Vergadi *et al*., 2017; Hansen *et al*., 2018; Serbulea *et al*., 2018).

NF-κB signaling pathway is a major pathway regulating immune and inflammatory responses. The activation of this pathway in monocytes and macrophages by CRP can lead to the production of pro-inflammatory cytokines, chemokines, and other inflammatory mediators. Pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-α, can promote tumor growth, angiogenesis, tumor cell survival, proliferation, and resistance to apoptosis (Kumar *et al*., 2009; Takeuchi and Akira, 2010; Gong *et al*., 2020). As other inflammatory mediators, such as prostaglandins and MMPs, are increased due to CRP-induced NF-κB activation, leading to angiogenesis, tumor immune evasion, tissue remodeling, tumor invasion, and metastasis (Terada *et al*., 1990; Overall and Lopez-Otin, 2002).

The phosphatidylinositol 3-kinase (PI3K)/AKT pathway is a crucial intracellular signaling pathway involved in various cellular processes, such as cell survival, proliferation, and inflammation (Li *et al*., 2014; He *et al*., 2021). Upon activation by CRP, PI3K phosphorylates the lipid phosphatidylinositol 4,5-bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 acts as a second messenger and recruits AKT (also known as protein kinase B) to the cell membrane. The recruitment of AKT to the cell membrane enables its phosphorylation at two critical sites: threonine 308 (Thr308) by phosphoinositide-dependent kinase 1 (PDK1) and serine 473 (Ser473) by mammalian target of rapamycin complex 2 (Engelman *et al*., 2006; Manning and Cantley, 2007). Once activated, AKT phosphorylates and regulates numerous downstream targets involved in cell survival, proliferation, and inflammation (Manning and Cantley, 2007). The PI3K/AKT pathway's dynamic regulation and its impact on various cellular processes make it an essential signaling pathway with potential implications in disease and therapeutic development. CRP promotes cell survival by activating the PI3K/AKT pathway and regulates inflammatory responses in macrophages and monocytes (Newling *et al*., 2019). This activation of the PI3K/AKT pathway plays a role in various physiological and pathological processes, including immune responses, tissue remodeling, and inflammation. It is essential to acknowledge that the effects of CRP on these signaling molecules can vary depending on the cellular context, CRP concentration, and other influencing factors. Furthermore, CRP can exert direct effects on these signaling pathways as well as indirect effects through its interactions with other molecules and cells in the microenvironment.

ATHEROSCLEROSIS

Atherosclerosis accounts for approximately 50% of deaths related to stroke and cardiovascular diseases (Tabas *et al*., 2015; Liu *et al*., 2016). Its incidence continues to rise as strong risk factors such as hypertension, obesity, type 2 diabetes, alcohol consumption, and smoking, increase (Verma *et al*., 2012; Martín-Timón *et al*., 2014). Vascular inflammation plays an important role in all stages of atherosclerosis, from initiation and the progression of atherosclerotic lesions to plaque rupture (Libby, 2002). CRP contributes to the initiation and progression of atherosclerosis by promoting endothelial cell activation and the recruitment of macrophages (Bisoendial *et al*., 2010; Grad and Danenberg, 2013). CRP primarily binds to cell membrane IgG FcγRs, leading to the increased expression of macrophage chemoattractant protein 1 (MCP-1) and vascular cell adhesion molecule 1 (VCAM-1), which contribute to the development of atherosclerosis (Sundgren *et al*., 2011; Raaz-Schrauder *et al*., 2014). CRP also upregulates the production of reactive oxygen species (ROS) in endothelial cells, platelets, monocytes, and vascular smooth muscle cells through specific FcγRs (Singh *et al*., 2005; Zhang *et al*., 2012). In human primary venous endothelial cells, the signaling mechanism of atherosclerosis induction by CRP involves the upregulation of the TF pathway by activating NF-κB and ERK1/2 (Chen *et al*., 2009). CRP activated the NF-kB pathway in Human umbilical vein cells (HUVECs) and human aortic endothelial cells (HAECs), induced VCAM-1 expression through CD32, and promoted endothelial cell-monocyte interaction, thereby contributing to the development of atherosclerosis (Liang *et al*., 2006). CRP induced the expression of inflammatory genes for nitric oxide (NO) formation, MCP-1, IL-6, and inducible nitric oxide synthase (iNOS) in vascular smooth muscle cells (Hattori *et al*., 2003). Additionally, CRP increased the activation of transcription factors NF-κB and AP-1, which are associated with intracellular redox reactions, and enhanced the activity of MAP kinases through the TLR4-dependent signaling pathway, inducing TNF-α secretion via the p38 MAPK-TLR4 pathway (Chang *et al*., 2012). Thus, the activation of these signals represents a significant risk factor for atherosclerosis and cardiovascular diseases.

The NLR family pyrin domain-containing (NLRP) 3 inflammasome is a multiprotein cytosolic complex that activates

the IL-1 family and plays an important role in atherosclerosis. A meta-analysis of genome-wide association studies identified NLRP3 as a predictor of CRP levels (Dehghan *et al*., 2011). CRP increased the expression of pro-IL-1β and NLRP3 through the FcγRs/NF-κB pathway in endothelial cells. It also promoted NLRP3 inflammasome activation and IL-1β maturation by upregulating ROS levels, purinergic receptor signaling, and the activation of cysteine proteases (Bian *et al*., 2019; Prakash *et al*., 2023). These findings indicate an association between elevated levels of CRP and NLRP3 inflammasomes in atherosclerosis. Therefore, inhibiting CRP can represent a new approach to the prevention and treatment of cardiovascular diseases.

Multiple experiments and clinical studies have consistently demonstrated the significant role of TF in the pathogenesis of acute coronary syndrome. TF is known to induce the formation of intracoronary thrombus following endothelial injury (Wilcox *et al*., 1989; Pawashe *et al*., 1994; Annex *et al*., 1995). Interestingly, cells that are not typically exposed to flowing blood, such as smooth muscle cells, express TF constitutively on their surface (Schecter *et al*., 1997; van den Eijnden *et al*., 1997). In contrast, cells that are in direct contact with the bloodstream, like endothelial cells, express TF only on their membrane. CRP was reported to induce the expression of TF in both endothelial and smooth muscle cells, which are widely present in the arterial wall. Moreover, the effect of CRP on TF expression was dose-dependent. CRP-induced TF expression in endothelial cell appears to occur through a direct effect of CRP, while in human monocytes, it requires cell-cell interactions with leukocytes (Paffen *et al*., 2004). The induction of TF expression by CRP is mediated through the activation of the NF-κB transcription factor via the ERK 1/2 pathway. In fact, the selective NF-κB inhibitor pyrrolidine dithiocarbamate (PDTC) significantly reduced CRP-induced TF expression. Interestingly, low concentrations of CRP could activate NF-κB in endothelial cells, whereas, in vascular smooth muscle cells (SMCs), this phenomenon occurred only at higher CRP concentrations. These different patterns of NF-κB activation in the two cell populations may explain their differential sensitivity to CRP-induced TF expression (Cirillo *et al*., 2005). The finding that CRP induces TF expression by activating of NF-κB can provide a partial explanation for the observation that patients with acute coronary syndrome and elevated CRP serum levels tend to experience worse clinical outcomes compared to those with normal CRP levels.

CONCLUSIONS

A chronic inflammatory state has been suggested to create an inflammatory microenvironment that predisposes individuals to cancer (Asegaonkar *et al*., 2015). Many studies suggested that CRP not only plays a role as an indicator of inflammation but also possesses significant pro-inflammatory characteristics (Pasceri *et al*., 2000, 2001). Elevated CRP levels have been associated with poor outcomes, abnormal metabolism, hypoalbuminemia, anemia, a wide range of diseases, and increased serum IL-6 levels (Falconer *et al*., 1995; Nakachi *et al*., 2007; Pine *et al*., 2009; Argilés *et al*., 2011).

This review summarizes the role and signaling pathways of CRP in various cancer and tumor microenvironment (Fig. 1). (1) The molecular link between the inflammatory lipid S1P and CRP is crucial in the increased invasive phenotype and tumor formation of TNBC cells (Kim *et al*., 2018). Elevated serum CRP levels are closely associated with breast cancer invasion, metastasis, and poor prognosis. (2) CRP induces IL-6 production in pancreatic tumors and activates the IL-6/AKT/STAT3 signaling axis, thereby promoting tumor progression. (3) CRP promotes the development of renal cell carcinoma by increasing the autophagy-related molecule ATG9B. (4) CRP is produced in the liver by IL-1β and IL-6, and regulates inflammatory responses and LDL metabolism. (5) CRP induces the F3-TF-ETS1-CCL2 axis and VEGF expression, leading to increased endothelial cell tube formation and angiogenesis. Additionally, CRP interacts with various cells within the tumor microenvironment, contributing to the initiation and progression of atherosclerosis. (6) CRP contributes to immunity, inflammatory responses, and tumor development by regulating the activity of various signaling molecules in macrophages and monocytes. Comprehending the interaction between CRP signaling pathways and other inflammatory mediators is crucial for unraveling the complex relationship between inflammation and cancer. This review can offer valuable insight into the role of CRP in various pathological conditions and potential therapeutic strategies targeting this pathway.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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