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REVIEW

C-reactive protein in gallbladder diseases: diagnostic and therapeutic insights

Ibraheem M. Rajab[1]✉, Daniel Majerczyk[1], Margaret E. Olson[1], Jenna M. B. Addams[1], Mihee L. Choe[1], Matthew S. Nelson[1], Lawrence A. Potempa[1]✉

[1] College of Pharmacy, Roosevelt University, Schaumburg, IL 60173, USA

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Abstract The gallbladder is an important component of the hepatobiliary system whose primary function is to aid in digestion of foodstuffs, excretion of drugs and facilitate removal of waste products from the body. The gall bladder is principally a storage organ for bile, chemically modified salts and acids of cholesterol which are synthesized in the liver and which function as surfactants to solubilize fatty substances of limited aqueous solubility. Any disruption in the amount or activity of bile surfactant can lead to an accumulation of insoluble molecular clumps (*e.g.,* gallstones) that deposit in and obstruct fluid movement within the gallbladder, and which can lead to pathological congestion and tissue damage. The natural host defense response to any event that causes tissue damage is to stimulate inflammation, which non-specifically but aggressively reacts to the stimuli so to remove the cause and repair damaged tissues. The C-reactive protein (CRP) is a primarily hepatically produced serum protein whose blood levels increase within 6–10 h of any tissue-damaging event. The extent with which it increases correlates with the level of tissue damage and associated inflammation. CRP levels are reported to be of value in diagnosing acute cholecystitis severity, in predicting the outcome and prognosis of cancer-associated gallbladder resection, and in helping identify cystic structures during emergency laparoscopic cholecystectomies. As an understanding of distinctive CRP structural isoforms is evolving, its role not only as a biomarker but as regulator of both physiologic and pathophysiologic processes of inflammation may be relevant in the understanding of and treatment approaches for gallbladder-associated disease.

Keywords C-reactive protein, Monomeric C-reactive, Inflammation, Gallbladder, Gallstone, Cholecystitis, Cholesterol

INTRODUCTION

The gallbladder is an important organ of the human digestive tract. Located beneath the liver, its primary function is to store bile salts and acids which serve as surfactants of dietary fats and oils during the process of digestion. Bile salts and acids, such as cholic acid and chenodeoxycholic acid and their conjugated glycine and taurine analogs, are synthesized from cholesterol in the liver. During digestion, these molecules are transported from the gallbladder through the common bile duct past the pancreas, where they empty into the duodenum and assist in the solubilization of non-polar molecules that enter into the gastrointestinal tract (Di Ciaula *et al*. 2017). Certain lipophilic and high molecular weight drugs (*e.g.*, mycophenolic acid, warfarin, and digoxin) and/or their metabolites are known to be excreted by forming complexes with bile. Such bile conjugates significantly impact drug systemic exposure, pharmacological effects, and toxicity (Ghibellini *et al*. 2006).

There are many diseases known to involve the gallbladder, the most common being caused by the formation of gallstones—insoluble fatty deposits containing

✉ Correspondence: irajab@roosevelt.edu (I. M. Rajab), lpotempa01@roosevelt.edu (L. A. Potempa)

cholesterol, bile pigments, bilirubin, calcium salts, and phospholipids (Ibrahim *et al*. 2018). These fatty deposits clump into waxy masses of varying size, which could lead to congestion of the organ and the bile duct. As the size and extent of waxy deposits grow, organ tissues can get stretched and damaged and lead to perforation in extreme cases, triggering a host defense response that is geared at removing the deposits and repairing the damaged tissues. Most fundamentally, these natural host defense responses involve inflammation, which can be acute or chronic, and which can cause pain and abdominal discomfort. Inflammation that affects the gallbladder itself is a condition known as cholecystitis. Inflammation that involves the bile duct is known as cholangitis. Because of the proximity to the pancreas and liver, gallbladder congestion may also cause pancreatitis and lead to hepatic obstruction and jaundice. Damaged gallbladder tissues have also been reported to be sites of infections and abscesses, cancers and necrosis (Stinton and Shaffer 2012), and patients with a medical history of gallstone disease may have increased risk of developing cardiovascular disease (Fairfield *et al*. 2019; Fan *et al*. 2017). Gallbladder congestion can also prevent secretion of bile into the duodenum and adversely affect absorption of certain vitamins and fats (Di Ciaula *et al*. 2017; Thompson 1971).

Acute cholecystitis refers to the rapid onset of gallbladder inflammation. In response to trauma caused by gallstone blockage, prostaglandins I_2 and E_2 are synthesized from arachidonic acid released from membrane phospholipids by phospholipase A_2 (PLA_2) and metabolized by the sequential actions of respective synthases such as cyclooxygenase (COX). These lipid hormones are locally acting potent stimulators of inflammatory processes (Ricciotti and FitzGerald 2011). As inflammation is non-specific to its cause, mediators such as histamine and reactive oxygen species are released into affected tissues, leading to neural and muscular damage (Pozo *et al*. 2004). In about 20% of acute cholecystitis cases confounding bacterial infection occur, most commonly involving *Escherichia coli, Klebsiella, Streptococcus, Clostridium, Staphylococcus faecalis, Clostridium perfringens,* and *Helicobacter Pylori* (Cen *et al*. 2018; Gouma and Obertop 1992; Juvonen *et al*. 1992). Until the infection is controlled and removed, the growth and expansion of both the bacterial colonies and the amassing host defense cells associated with the inflammatory response can lead to pronounced swelling secondary to the trauma affecting the gallbladder wall.

Chronic cholecystitis is gallbladder inflammation that persists because of multiple recurring episodes of gallstone deposits, unresolved removal of fatty deposits, and unrepaired tissue damage. Generally, chronic inflammation involves a weak or unamplified inflammatory response, leading to production and release of lower levels of inflammatory mediators that get released into affected tissues. Chronic cholecystitis can be more difficult to diagnose than acute cholecystitis, as the level of pain and discomfort caused by the inflammatory response may be vague enough or asymptomatic enough so the patient and healthcare provides ignore or misdiagnose the disease. Chronic cholecystitis can be complicated by many concomitant issues, such as empyema, hydrops, gangrene, fistulas, or limey bile. Calcium may also deposit and harden in the walls of the gallbladder, causing extensive scarring (Elwood 2008; Greenberger and Paumgartner 2018; Lee and Boll 2018).

Reported prevalence of gallstone disease in the adult United States population is 10%–15% (Ibrahim *et al*. 2018) and 5%–25% of adults in the Western world (Gurusamy and Davidson 2014). Prevalence varies worldwide between different ethnic groups due to variable genetic and environmental factors (Di Ciaula and Portincasa 2018; Hernandez-Nazara *et al*. 2006; Stinton and Shaffer 2012).

While both acute and chronic inflammations are fundamentally linked to the pathophysiology of gallbladder diseases, little focus has been given to the role of inflammatory markers in diagnosing and assessing the extent of tissue-damaging processes occurring as part of these diseases. This report will summarize how the prototypic acute phase reactant—C-reactive protein (CRP)—may be a useful marker for disease activity. It will also introduce novel concepts involving heretofore unappreciated structural isoforms of CRP and the distinct biofunction(s) of each as a regulator of inflammatory processes.

INFLAMMATION AND THE GALLBLADDER

Acute gallbladder inflammation (cholecystitis) is triggered by three main mechanisms: (1) obstruction of the organ and/or the cystic duct by the formation of gallstones, and the subsequent tissue damage that occurs concurrent with their formation; (2) release of "lysolecithin", a fatty acyl chain from the C2 position of glycerol phospholipids with the associated formation of lysophosphatidyl choline (LysoPC) from membrane lipids, and (3) ascending bacterial infection of the biliary fluid most notably caused by gallstones obstruction (Schuld and Glanemann 2015).

The formation of gallstones occurs when (1) Bile becomes supersaturated with cholesterol;

(2) Cholesterol molecules nucleate, changing their organization in a way that causes them to crystalize and grow into insoluble stones; (3) Gallbladder motor function becomes abnormal, reducing emptying of bile into the bile duct and duodenum (leading to bile stasis); or (4) Gastrointestinal hypomobility which reduces enterohepatic cycling of bile salts. The risk of forming insoluble gallstones is directly related to the concentration of cholesterol found in the gallbladder and is inversely related to the concentration of the more amphipathic biliary salt conjugates and to phospholipids. Cholesterol has been implicated in both formation of gallstones and in gallbladder hypomotility (Hernandez-Nazara *et al*. 2006).

At local sites of tissue damage, one of the first biochemical responses in the hydrolysis of a fatty acyl chain from the C2 carbon of a diacyl glycerol phospholipid. This hydrolysis is mediated by the enzyme phospholipase A_2 (PLA_2), an enzyme that, while not known as an acute phase reactant, is tightly associated with the onset of early and robust inflammatory responses. There are several isoforms of PLA_2 which differ in distribution and function. The isoform cytosolic PLA_2 is induced by inflammatory cytokines such as TNF-α and is known to strongly regulate inflammation (Leslie 2015; Yarla *et al*. 2016). This, in part, is mediated by the release of arachidonic acid from membrane lipids, which enters into eicosanoid pathways using cycooxygenase enzymes (COX) or lipoxygenase enzymes, generating potent prostaglandins or leukotriene lipid inflammatory mediators. After the acyl chain is cleaved from the diacyl glycerol lipid, the remaining monoacyl glycerol lipid (known as a Lysolipid) has a significant change to its hydrophilic–lipophilic balance (HLB), effectively emulsifying and/or solubilizing the membrane bilayer where it is produced (Pichot *et al*. 2013). The disruption in the bilayer results in a change in the thickness and the curvature of the bilayer, and results in a lateral redistribution of intramembrane components including cholesterol, which can associate into cholesterol-rich microdomains known as lipid rafts (Cheng and Smith 2019; Marquardt *et al*. 2016). Lysophosphatidyl choline (*i.e*., LysoPC) expressed at activated membrane sites becomes a beacon for platelet and neutrophil accumulation and activation. COX inhibitors such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDS), lessen the production of prostaglandins which reduces the inflammation and pain associated with a stimulated inflammatory response.

Since PLA_2 is also a key enzyme in the activation and progression of an inflammation, inhibiting or otherwise controlling this enzyme is also being evaluated as an effective mechanism for controlling the inflammatory response (Caprio *et al*. 2018). Indeed, the purported anti-inflammatory activity associated with drinking red wine may involve the inhibition of PLA_2 activity by resveratrol, a key compound found in red wine and various vegetables (Fei *et al*. 2018). Changes in membrane thickness, curvature, and cholesterol content can affect the insertion of peptides into a membrane, which in turn, can alter cellular responses involving signaling mechanisms (Haque and Lentz 2004; Karabadzhak *et al*. 2018; Lähdesmäki *et al*. 2010).

DIAGNOSIS OF GALLBLADDER PATHOLOGIES

Symptoms of acute cholecystitis typically include biliary pain, nausea, and vomiting. Biliary pain can manifest as right upper quadrant pain and radiate to the right scapula or shoulder. The right upper quadrant of patients experiencing an acute cholecystitis attack will be tender and sore upon palpation. Abdominal stiffness and chills may also arise with attack. The symptoms typically subside after 2–3 days and resolve after a week but can lead to increasing pain, perforation or abscesses.

Cholecystitis may also present with abdominal soreness or tenderness, fever, and leukocytosis. Jaundice, dark urine, or light-colored stools can be observed when the common bile duct becomes obstructed, leading to incomplete conjugation of the heme breakdown product—bilirubin in the liver and the resultant release of excess bilirubin into the blood. In some cases, involving excessive liver involvement, aminotransferase enzymes (*e.g*., aspartate amino transferase (AST)) may be released into the serum, which is easily monitored as part of a routine metabolic panel test.

An ultrasound of the right upper quadrant is another diagnostic tool that may be useful. An ultrasound could show signs of wall thickening, fluid buildup, dilatation of the bile duct, or contraction of the gallbladder while fasting. Performing this test with fasting helps minimize confounding interpretations related to active gallbladder function and movement of bile contents from the gallbladder, through the common duct and into the duodenum. If symptoms and other diagnostic tests are inconclusive, a radionuclide (HIDA) scan may be ordered. The HIDA scan shows the radioactivity of the injected radionuclide within the bile duct but does not allow visualization of the gallbladder. The radionuclide may also settle into the gallbladder and not be released upon the patient consuming a fatty cream. This test can be used to show both gallbladder duct obstruction and poor gallbladder function (Elwood 2008; Greenberger and Paumgartner 2018; Lee and Boll 2018).

Cholecystitis is a progressive disease that requires continued monitoring and treatments based on its persistence and severity. The most commonly used diagnostic tests to assess acute cholecystitis include liver function tests to evaluate liver damage, and leukocyte counts to assess the status of the inflammatory response (higher leukocyte counts are reflective of an active inflammatory response). Another blood marker reflective of the presence and extent of inflammation is C-reactive protein (CRP), widely known as a non-specific serum-based marker. Even though the exact role of CRP as a regulator of inflammation remains unknown, its inclusion as a diagnostic marker to assess aspects of gallbladder disease was recommended by the 2007 Tokyo guideline criteria (Hirota *et al*. 2007) and was reinforced in 2018 (Kiriyama *et al*. 2018). A retrospective study reported a strong correlation between CRP levels and the grade of acute cholecystitis, suggesting CRP may also be a useful marker to diagnose not only the presence of, but the staging of disease (Gurbulak *et al*. 2015).

As advances in understanding CRP structure–function relationships have occurred, its presence, concentration, and short-term changes in blood levels are added increased value to healthcare personnel in understanding and treating gallbladder disease. The simplicity, relatively safety of gathering blood samples, and the economic value of ordering CRP tests should be included in routine monitoring of disease activity and the responses to treatments used on afflicted patients. Indeed, simple CRP measurements are preferred options to imaging methods or more invasive procedures.

CRP AS THE PROTOTYPIC DIAGNOSTIC MARKER OF THE ACUTE PHASE RESPONSE AND ENSUING INFLAMMATION

Inflammation is the natural host defense response to any event that causes damage to body tissues (Fig. 1). The most immediate response to tissue damage is a survival response, which is activated to prevent life-threatening bleeding and to mobilize and localize leukocytes to respond to any threats introduced into the exposed tissues. The earliest phases of inflammation, occurring within seconds to minutes of the inciting cause, must not only be activated, but amplified to address the threat to life and homeostasis. Initially, these responses involve the bioactivities of certain proteins found in blood known as the acute phase reactants (APRs). APRs include blood clotting factors such as fibrinogen, opsonins such as complement protein C3, anti-proteases such as alpha-1 anti-trypsin, transport proteins such as haptoglobin, and wound healing factors such as fibroblast growth factor (Kushner *et al*. 2006). Because these proteins are rapidly consumed during the acute process, their quick replacement is critical, thus describing why such proteins are categorized as key reactants of the "acute phase". By monitoring their temporal changes in blood concentration as a function of the onset and duration of tissue insult, most APRs are seen to increase modestly (*i.e*., changing by percentage levels) or to small multiples of their normal levels (*e.g*., two-folds to four-fold increases). Two proteins are known, however, to increase up to several 100-fold (*i.e*., up to 500-fold) as part of the acute phase response. One of these proteins is the serum amyloid A protein (SAA), an apolipoprotein expressed on high density lipoprotein particles (Sack 2018). Because of its lipid association, isolating and quantifying SAA from serum has proven to be challenging but reports have appeared describing it can be used to differentiate passive and active movement of blood proteins into extravascular tissues (Okino *et al*. 2006). The second protein that can rapidly increase several 100-fold in response to tissue damage is C-reactive protein (CRP). CRP is a highly soluble, easy to quantify blood protein with a relative short half-life of 19 h (Vigushin *et al*. 1993). Its blood levels are related to its hepatic synthesis rate, persisting as long as cytokine signals (*i.e*., interleukin 6) continue to be produced by damaged tissues (MacIntyre *et al*. 1983; Sproston and Ashworth 2018). Because its blood levels correlate with any disease or trauma that involves tissue damage, CRP is widely known as the prototypic acute phase reactant. Because tissue damage always involves the stimulation of inflammation processes, the change in CRP levels in blood is commonly interpreted to be a key diagnostic marker for the presence and extent of inflammation.

Baseline levels of CRP vary from 1 to 3 μg/mL in most individuals. Blood levels are found to rise approximately 6–10 h after the inciting stimuli occurs (Pepys and Hirschfield 2003). Any blood level above 10 μg/mL is considered diagnostic of an ongoing inflammatory condition (FDA guideline 2005). The extent and duration of increased blood levels can provide useful diagnostic information in the care and treatment of affected patients. While blood CRP levels correlate with the extent of tissue-damaging inflammation, surprisingly there is no selective localization of CRP from blood into to tissue sites known to be involved with prominent inflammation (Vigushin *et al*. 1993). CRP reported fractional catabolic rate is independent of its plasma concentration indicating that the

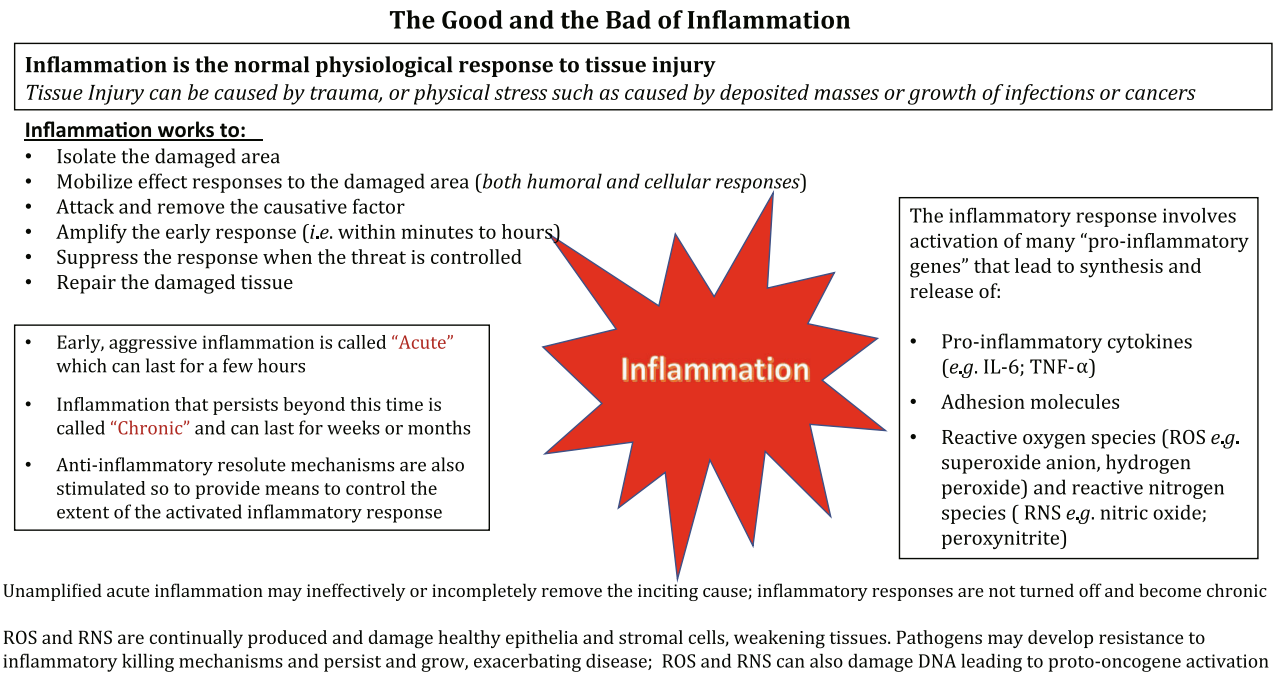

Fig. 1 Inflammation actions and reactions to body tissues damage. A process triggered immediately as survival technique and developed accordingly during the cytokine signal persisted communication

change in blood levels during an acute inflammatory response reflects on an increase in the synthesis rate of CRP rather than its consumption. CRP plasma levels above 100 μg/mL (*i.e.*, ∼ a 33 to 100-fold increase over baseline) are generally associated with severe tissue damage and robust inflammation. CRP levels that persist at and above this elevated level are considered a poor prognostic indicator and should be an index guiding decisions to use more aggressive medical interventions.

In recent years, significant focus has been placed on the diagnostic and prognostic significance of plasma CRP levels between baseline and 10 μg/mL (*i.e.*, below that value defined by the Food and Drug Administration of the United States (FDA) as diagnostically significant). These values are measured using what is known as a "high sensitivity CRP" assay (*i.e.*, hsCRP). While many studies implicate elevated hsCRP levels as an index of "micro-inflammation", and some studies suggest higher baseline hsCRP levels in different individuals may be predictive of disease risk (Antonelli and Kushner 2017), "high sensitivity" simply refers to the sensitivity of assays used to detect the very same molecule CRP, no studies are conclusive and the FDA makes no recommendation to the value or significance of hsCRP data (FDA Guideline 2005, updated on 3/13/18). Various reports have appeared suggesting higher baseline hsCRP levels in different individuals may be more related to genetic polymorphisms (*i.e.*, single base polymorphisms (SNPs)) in promoter regions of the gene coding for CRP (Su *et al*. 2014).

CRP AS A DIAGNOSTIC MARKER OF GALLBLADDER DISEASE

Use of CRP as a diagnostic marker for inflammatory gallbladder diseases has been relative uncommon (Hirota *et al*. 2007; Strasberg 2008). Some early studies did report that CRP measurements were more sensitive than erythrocyte sedimentation rates or white cell counts to support a cholecystitis diagnosis. Furthermore, when used in combination with ultrasonographic exams, CRP levels helped increase diagnostic accuracy of acute cholecystitis from 79% to 97% (Juvonen *et al*. 1992). While CRP was reported to be a useful marker for acute disease, it did not appear to be of benefit in diagnosing chronic disease (Beliaev *et al*. 2015).

When gallbladder disease presents with cancerous or gangrenous co-morbidities, CRP levels are found to be markedly elevated (Beliaev *et al*. 2015; Cui *et al*. 2018; Koshiol *et al*. 2016; Mok *et al*. 2014). CRP levels were described as a superior marker than leukocyte count as an index of disease activity (Beliaev *et al*. 2015; Shabanzadeh *et al*. 2016).

In efforts to normalize understanding of and treatment options for hepatobiliary diseases, Tokyo Guidelines were developed (2007) and updated (2018)

by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. The guidelines recommend that CRP levels >30 μg/mL be used to support a diagnostic of acute cholecystitis. This value further refines the FDA guideline in setting an index for diagnosing an acute episode of disease. Such guidelines support any CRP level >10 μg/mL as indicative of an activated inflammatory response in a patient, especially if elevated CRP levels are noted in conjunction with either a markedly decreased or increased leukocyte count (FDA guideline 2005). Hence, CRP levels of >30 μg/mL along with ultrasonographic findings consistent with acute cholecystitis, have a high sensitivity, specificity, and positive predictive value of 97%, 76%, and 95%, respectively, for aggressive, acute disease (Hirota *et al*. 2007).

CRP levels are also useful in assessing recurring or exacerbating disease, and possibly even fatal outcomes. Extremely high CRP levels (>100 μg/mL) that persistent with or without various treatments, are poor prognostic indicators. When the acute phase host defense response successfully controls the treat and tissues begin to heal, acute phase proteins should return to normal blood levels within days. As the threat is controlled and tissues heal, cytokine signals for CRP hepatic synthesis are no longer produced, and the synthesis and secretion of CRP into the blood slow. Because of its 19-h plasma half-life, measured blood levels should return to baseline over 3–4 days (Vigushin *et al*. 1993). CRP levels that remain persistently high for more than 4 days can be used to help diagnose treatment failures and significant, unresolved tissue damage. Seriously compromised tissues where disease persists will involve a prolonged, non-specific, robust inflammatory response which will add to and worsen tissue damage initially caused by the deposited gallstones. If left untreated, organ function will continue to decrease, threatening survival.

Additional criteria used to assess the severity of acute cholecystitis include the CRP/albumin ratio (CRP/Alb), neutrophil/lymphocyte ratio (NLR), the Glasgow prognosis score (GPS), and modified Glasgow prognosis score (mGPS). Each of these independently predict a severity grade (*e.g*., moderate or severe), which can be used in combination with clinical, laboratory, and imaging findings to assess disease activity. The GPS score in part includes a CRP-based value which, in accordance with the Tokyo Guidelines, indicates CRP does play a complementary role in assessing the severity of acute cholecystitis (Sato *et al*. 2018). The GPS score has also been used to predict outcomes of gallbladder resection performed as a treatment for gallbladder cancer. GPS scores that reflect low albumin and elevated CRP levels, used in conjunction with advanced tumor stage and positive lymph node metastasis, was predictive of cancer recurrence and overall survival (Shiba *et al*. 2015).

For both acute and chronic cholecystitis, surgical intervention is the current preferred therapy when indicated by symptoms or complications. The most common intervention is cholecystectomy, or complete removal of the gallbladder from the body. This is often accompanied, either before or after surgery, by a course of antibiotics against Gram-negative organisms that may have been present in the inflamed gallbladder. Emergency cholecystectomy is preferred in patients with potentially severe complications, such as empyema, gangrene, or perforation. Cholecystectomies are otherwise an elective surgery, usually performed laparoscopically in a preferred time frame of 48–72 h after diagnosis. The delay of elective cholecystectomy from the time of diagnosis has not been shown to increase risk of complications from either surgery or acute cholecystitis. Cholecystectomies are relatively safe procedures and provide symptom relief in 75%–90% of patients (Elwood 2008; Greenberger and Paumgartner 2018; Lee and Boll 2018; Okamoto *et al*. 2018).

CRP levels have also been used to assess a critical view of safety (CVS) during laparoscopic cholecystectomy in patients presenting with acute cholecystitis. The CVS is described as a method to identify cystic structures during the surgery, enhancing patient safety through correct identification of all structures critical to the operation. A scoring system based on the three preoperative factors, including CRP levels, was found to be an effective evaluation of the likelihood that CVS can be achieved, and patient safety can be enhanced during emergency cholecystectomy. Preoperative CRP levels of >55 μg/mL, along with gallstone impaction and greater than 72 h between symptom onset and time at which surgery is performed, correlate with an inability to achieve CVS. Thus, elevated CRP levels may be indicative of poor patient prognosis (Onoe *et al*. 2017).

Table 1 summarizes published reports of CRP levels in various gallbladder diseases. These reports underscore and emphasize that the disease/complication severity grade and inflammation seen with gallbladder diseases correlate with extremely high CRP values (>100 μg/mL).

Because of its intimate connection to the presence of any inflammatory response, no matter what was the primary cause that stimulated the inflammation, CRP testing has been used (in conjunction with other tests) by physicians to help make diagnostic decisions regarding infections, heart disease, bowel disease, rheumatoid arthritis, systemic lupus erythematosus and other diseases. Most basically, medical community

Table 1 Reported CRP values in gallstone relevant diseases

Condition	C-reactive protein (μg/mL)	References	Study type
Acute cholecystitis with pathogenic organism growth from bile	130	Juvonen *et al.* (1992)	Research
Acute cholecystitis with bile culture showed no growth	77		
Acute cholecystitis with Gallbladder gangrenous	146		
Acute cholecystitis with Gallbladder not gangrenous	78		
Acute cholecystitis complicating mumps	248	Brent *et al.* (2006)	Case report
Acalculous cholecystitis	231.7	Goodier *et al.* (2012)	Case report
Acalculous cholecystitis in 14-year old boy	Day1:176, Day3: 384	Shreders and Michie (2010)	Case report
Systemic lupus erythematosus with acute acalculous cholecystitis	137.8	Choi *et al.* (2014)	Case report
Acalculous cholecystitis in a 7-year-old child	301	Ng and Gu (2018)	Case report
Diagnostic criteria and severity assessment of acute cholecystitis	30 or more	Hirota *et al.* (2007)	Tokyo Guidelines
Prediction of the grade of acute cholecystitis (cut-off)	Mild: 18.96, Moderate:70.65, Severe: 198.95	Gurbulak *et al.* (2015)	Retrospective research
Acute cholecystitis	76.6	Akimoto *et al.* (2016)	Case report
Acute cholecystitis	Greater than 120	Nizri *et al.* (2016)	Research
Acute calculous cholecystitis	≥110	Díaz-Flores *et al.* (2017)	Multivariate analysis
Acute cholecystitis: increased operation length	More than 50	Yamamoto *et al.* (2017)	Research
Evaluation of severity of acute cholecystitis (cut-off)	Mild: 7, Moderate: 15, Severe: 53	Yuzbasioglu *et al.* (2017)	Research
Acute cholecystitis	More than 36	Teckchandani *et al.* (2010)	Research
Acute complicated cholecystitis	Normal cholecystectomy: 4.4, Acute cholecystitis: 28.5, Gangrenous cholecystitis: 153.6	Ay and Tanrikulu (2019)	Research
Gangrenous cholecystitis	148	Chaudhry *et al.* (2011)	Case report
Gangrenous cholecystitis, optimal cut-point	≥123	Cui *et al.* (2018)	Retrospective cohort study
Severe/gangrenous cholecystitis	More than 200	Mok *et al.* (2014)	Research
Symptomatic cholelithiasis	Statin use: 112; No statin: 113	Pulkkinen *et al.* (2014)	Research
Cholecystomucoclasis	181	Tsukada *et al.* (2012)	Research
Eosinophilic cholecystitis	149.12	del-Moral-Martínez *et al.* (2015)	Case report
Predictive factor for a prolonged operation in laparoscopic cholecystectomy performed after percutaneous transhepatic gallbladder drainage	213	Lee *et al.* (2017)	Observational study
Laparoscopic cholecystectomy in acute cholecystitis	More than 165	Wevers *et al.* (2013)	Multivariate analysis
Predictor of conversion of laparoscopic cholecystectomies	>220	Mok *et al.* (2016)	Research
The bile of patients with gallbladder diseases	6–48	Vaishnavi *et al.* (2004)	Research
Preoperative CRP is an independent predictor of a technically more difficult cholecystectomy in the emergency setting	>100	Gregory *et al.* (2019)	Research

Published concentrations are all converted to μg/mL units in this table for facilitated comparison. FDA guideline cut-off for diagnosing inflammation = 10 μg/mL. Tokyo guideline cut-off for diagnosing acute inflammation = 30 μg/mL

consensus is that the CRP levels should not be used as a singular diagnostic tool, but rather as a supportive index with other diagnostic findings, to help provide guidance in the care and treatment of patients. The medical community has primarily defined CRP as a non-specific biomarker of inflammation. More correctly, CRP should be viewed as a clinical biomarker for the presence of and severity of tissue damage that accompanies any disease or significant trauma to tissue structures and functions. Since, inflammation is a natural response to tissue damage, CRP levels do represent an index of the extent of inflammation. Extremely high levels are prognostic of severely damaged, seriously compromised tissues, which are more difficult to control, repair, and return to healthful homeostasis. An inability to control and repair such tissues can explain why persistently elevated CRP levels often correlate to worse outcomes (Wu *et al*. 2015).

INSIGHTS INTO THE BIOLOGICAL FUNCTION(S) OF CRP

For more than a half-century since CRP was first identified as a protein "not normally found in blood" but occurring during "acute infections" (Abernathy and Avery 1941; Macleod and Avery 1941a, b), scientists have attempted to describe a biofunction for CRP related to its occurrence during host defense responses involving inflammation. Most generally, CRP has been studied as a protein that could enhance phagocytosis, accelerate chemotaxis, and promote the activation of platelets, all reactions occurring during the earliest phases of the acute inflammatory response. As CRP levels were found to elevate as a function of the presence and extent of inflammation associated with any disease (*i.e*., it was not selectively produced in response to infectious diseases), it has been viewed as a factor somehow involved in general reactions and pathologies associated with inflammation, including both acute and chronic inflammatory responses.

CRP was initially discovered as a protein that precipitated with a polysaccharide cell wall fraction (fraction "C") isolated from Gram positive *Streptococcus pneumonia* organisms by (Tillet and Francis 1930). The protein reactive with the "C" polysaccharide fraction (hence, the "C-substance"-reactive protein) demonstrated calcium-dependent binding for the phosphocholine moiety expressed in the gram-positive bacterial cell wall teichoic acid (Gotschlich *et al*. 1982). CRP was later shown to be a non-glycosylated, non-covalently associated cyclic pentameric protein with each subunit being 23 kDa and being arranged in a discoid orientation surrounding a central void (Shrive *et al*. 1996; Srinivasan *et al*. 1994) (see Fig. 2A for a space-filling depiction). In detailed protein structural studies, CRP was categorized as a member of the pentraxin protein family, which includes the serum amyloid P protein (SAP) and the long pentraxin 3 (PTX3), neural pentraxin I (NPI) and II (NPII) (Hsu and Perin 1995; Omeis *et al*. 1996).

CRP homologues have been widely found in evolution extending back to the horseshoe crab where the protein limulin shows 30% sequence homology to human CRP and shares at least one antigenic epitope (Pathak and Agrawal 2019; Ying *et al*. 1992). While human CRP is an acute phase reactant, defined as any protein whose blood level changes rapidly in association with a stimulate host defense response, it is a constitutive protein in some lower species, being found, for example, at about 500 μg/mL in the rat which is about 50–100 times higher than the concentration in humans (Padilla *et al*. 2003).

Each subunit of CRP contains 206 amino acids and includes one intrachain disulfide bond connecting the only 2 cysteine residues in the CRP subunit primary sequence. In its pentameric conformation (*i.e*., pentameric CRP or pCRP), subunits are held together by strong apolar and electrostatic forces which help the pentamer assume a tightly packed protein conformation that, while being freely soluble in aqueous solutions, packs so tightly and it resists proteolysis with commonly used proteases (Kinoshita *et al*. 1989).

Each subunit has a shallow, calcium-dependent binding pocket for ligands presenting phosphocholine (PC) ligands (such as the C-polysaccharide cell wall as discussed above). Each PC binding site is expressed on the same "face" of the discoid protein such that, when CRP binds to surfaces expressing many PC ligands, the CRP pentamer (pCRP) orients "flat" on the PC binding surface, asymmetrically juxtaposing its PC binding face to the surface expressing PC groups, and allowing its opposite face (described as the CRP helical or effector face) to be accessible to cells and factors that will contribute to effector responses activated in response to CRP binding (See Fig. 2B, C). In this way, CRP is an opsonin—making a target surface and triggering a host defense response against the target. CRPs immobilized on PC ligands are known to activate the classical complement pathway and to stimulate phagocytosis (Summarized in Table 2; Deveraj *et al*. 2003; Du Clos *et al*. 1988, 1991; Jewell *et al*. 1993; Mihlan *et al*. 2009; Mold *et al*. 1999; Salonen *et al*. 1984; Singh *et al*. 2005; Swanson *et al*. 1989; Tseng and Mortensen 1988; Wu *et al*. 2015).

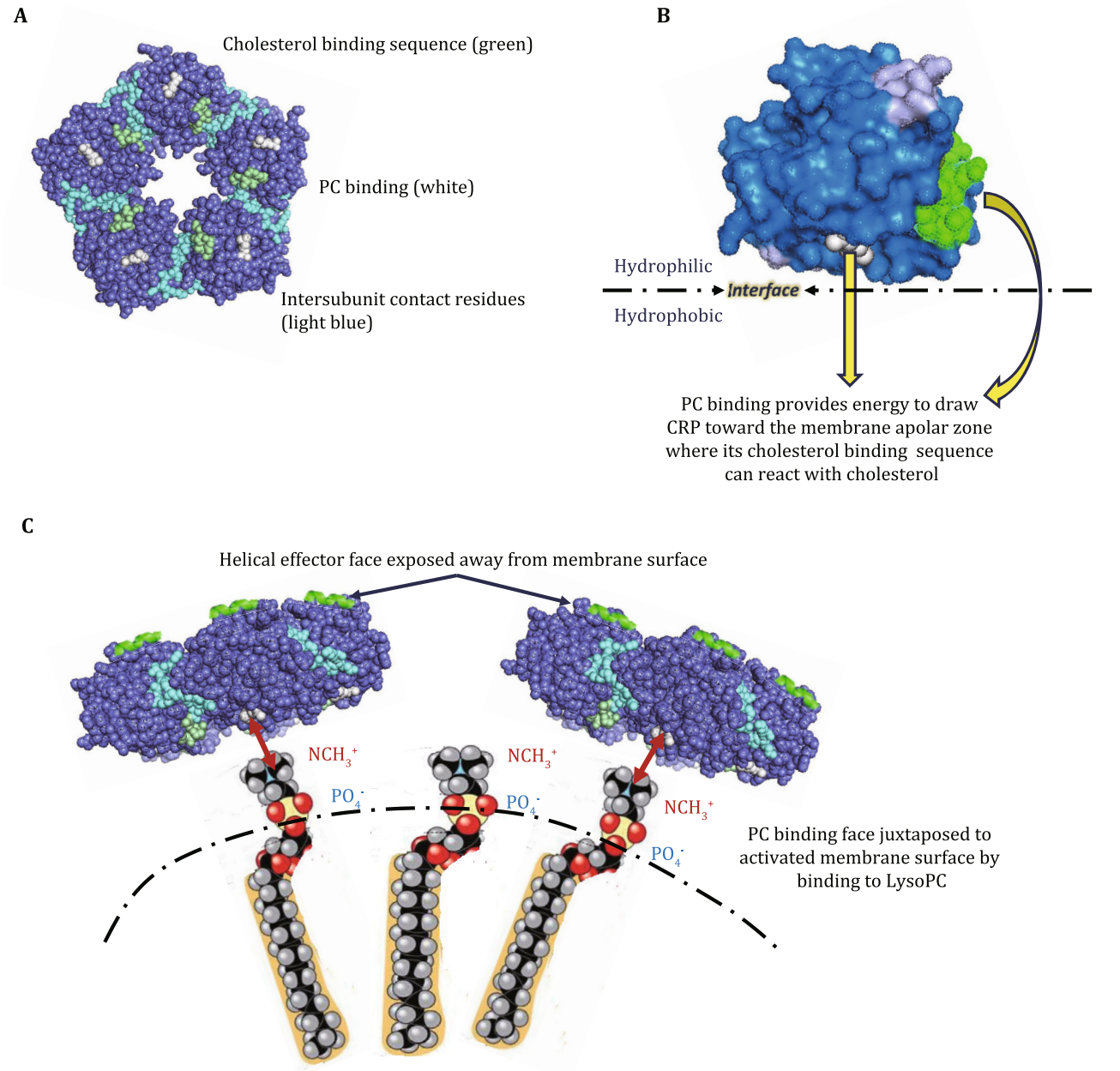

Fig. 2 **A** Visual orientation of PC binding sites, cholesterol binding sequences and residues contributing to stabilization of the pCRP isoform on the PC binding face of the discoid pentameric molecule (PDB code: 1B09). **B** Similarly visualized residues as in **A** depicted on an isolated CRP subunit. This depiction is included to show the special relationship between PC binding and cholesterol binding sites on an isolated pCRP subunit. It does not depict the orientation of residues on the mCRP isoform which changes structure when it binds cholesterol and enters into a lipid milieu. To date, structural coordinates for the mCRP isoform have not been established. **C** pCRP orients "flat" on the PC binding surface, asymmetrically juxtaposing its PC binding face to the surface expressing PC groups, and allowing its opposite face (described as the CRP helical or effector face) to be accessible to cells and factors that will contribute to effector responses activated in response to CRP binding

While widely recognized as the most prototypic protein representative of an ongoing acute phase response, its definitive role as a regulator of inflammation was not clearly established for decades after its discovery. Many directly conflicting conclusions described CRP as having both pro-inflammatory and anti-inflammatory activities and as being both anti-thrombotic and pro-thrombotic (Wu *et al.* 2015). Without truly understanding its biofunction, CRP was only perceived as a diagnostic marker of limited use in helping devise treatment strategies or in understanding disease pathologies.

Table 2 Distinctive characteristics of the pentameric CRP and monomeric CRP isoforms

Pentameric CRP (pCRP)		
Binding ligands	Bioeffect	Host defense effect
Phosphate monoesters (*e.g.*, Phosphocholine)	• Opsonization for phagocytosis	• Clearance of pathogenic substances
C1q and Factor H	• Regulates complement activation • Opsonization for phagocytosis	• Enhances recognition for efficient clearance of pathogenic substances
Fcγ receptors: FcγRII (CD32) and FcγRI (CD64)	• Inhibits eNOS, reducing vasodilation • Decreases PMN adherence to endothelial cells • Decreases diapedesis	• Blocks access of blood components to tissues • Anti-inflammatory
snRNPs and Histone	• Marks cell debris for clearance	• Clearance of cell debris
Plasminogen activator inhibitor (PAI)	• Inhibits fibrinolysis	• Prevents clot resorption
Fibronectin and Laminin	• Cell communication and activation	• Effects interactions of connective tissues and cells
Monomeric CRP (mCRP)		
Binding ligands	Bioeffect	Host defense effect
Cholesterol	• Binds and enters into lipid rafts • Activates cell signaling mechanisms • Increases transcription of pro-inflammatory factors	• Pro-inflammatory
Binds low-density lipoproteins	• Enhances uptake of nLDL by macrophages • Reduces uptake of oxLDL by macrophages	• Enhances recycling of normal LDLs • Reduces deposition of oxLDL into plaques
FcγRIII (CD16)	• Cell activation • Amplifies immune complex binding and processing by phagocytic cells	• Enhances clearance of antibody-marked antigens
C1q and Factor H	• Regulates complement activation	• Enhances recognition for efficient clearance of pathogenic substances
Platelets	• Increases platelet activation and formation of thrombi	• Prevents blood loss and walls off area of tissue damage
Leukocytes (PMNs and monocytes/macrophages)	• Upregulates CD11b/CD18 expresion • Increases PMN adherence to endothelial cells	• Amplifies vasoactive responses
	• Delays PMN apoptosis	• Prolongs activated acute phase responses
	• Increases PMN production of reactive oxygen species (ROS) and reactive nitrogen species (RNS)	• Amplifies neutrophil effector function to respond to threats introduced into damaged tissues
	• Increases production of interleukin-8 and MCP-1	• Recruits additional inflammatory cells to the tissue site • Pro-inflammatory
Brain	• Stimulates angiogenesis • Promotes tube formation	• Increase access to blood components

References: Wu *et al.* (2015), Braig *et al.* (2017), Deveraj *et al.* (2003), Du Clos *et al.* (1988, 1991), Jewell *et al.* (1993), McFadyen *et al.* (2018), Mihlan *et al.* (2009), Mold *et al.* (1999), Potempa *et al.* (2015), Salonen *et al.* (1984), Singh *et al.* (2005), Swanson *et al.* (1989), Tseng and Mortensen (1988)

DISCOVERY OF A MODIFIED, MONOMERIC ISOFORM OF CRP

Clarity in the biofunction of CRP was introduced in the 1990s with the discovery that the pentameric CRP structure could be induced to dissociate into monomeric subunits under physiologically relevant conditions. When the subunits are separated, biochemical energies are rapidly and irreversibly redistributed such that the globular subunits become modified into a unique structural isoform, described as a modified, monomeric CRP (*i.e.*, mCRP). mCRP derives from pCRP

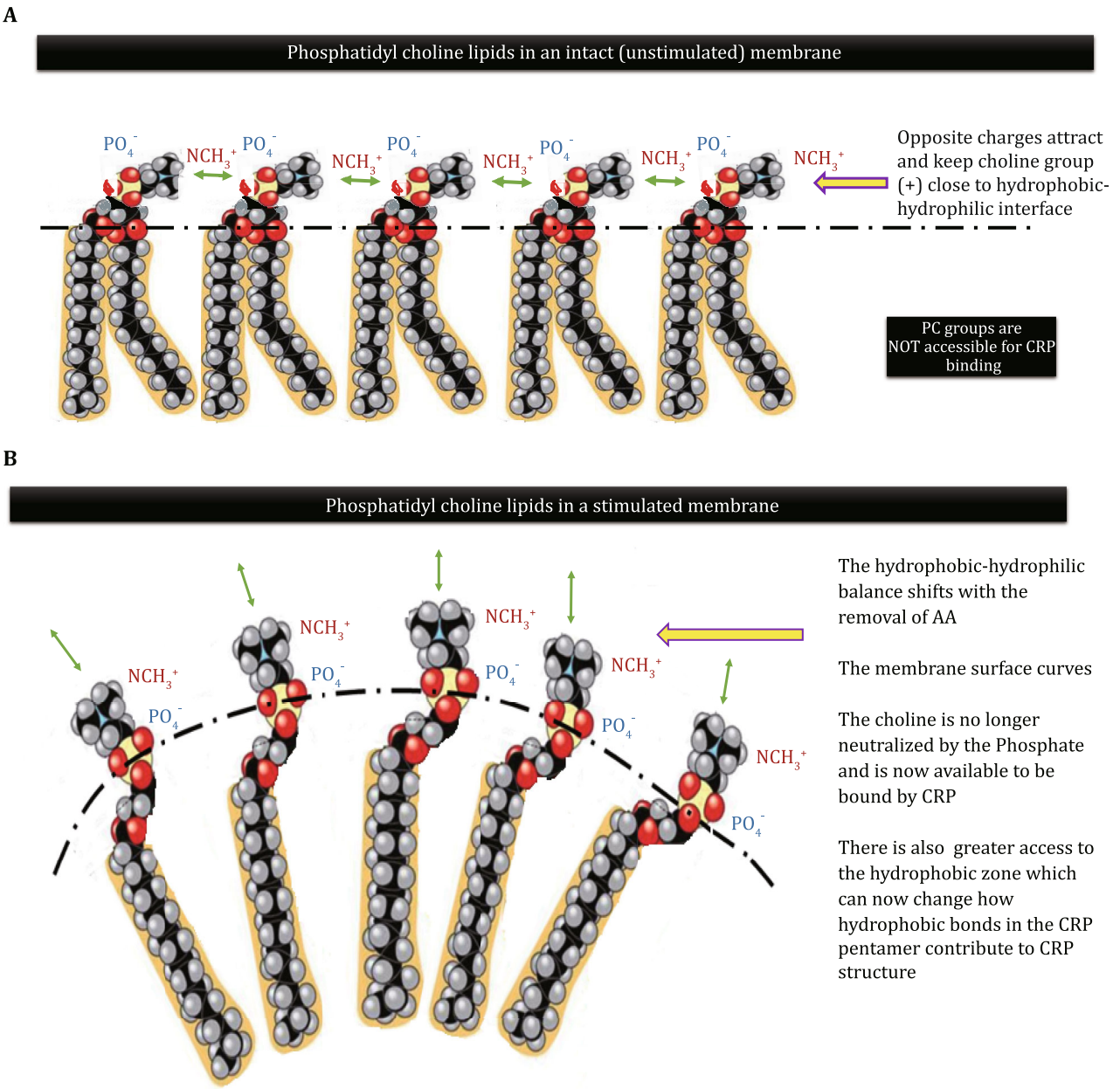

Fig. 3 PLA2 hydrolysis reaction of the diacyl lipid on the membrane surface. **A** Before. **B** After

by a non-proteolytic structural change that occurs when pCRP binds to PC groups on plasma membrane phosphatidylcholine lipids. This binding only occurs to exposed PC groups expressed at localized activated tissue sites when the enzyme phospholipase A_2 cleaves the C2 fatty acid off a diacyl lipid, producing monoacyl phosphatidylcholine molecule (*i.e.*, LysoPC) (Caprio *et al*. 2018). Figure 3 depicts how membrane surfaces and expression of phosphocholine groups are altered after PLA_2 cleaves a fatty acyl chain off a diacyl lipid. Because each pCRP subunit has a PC binding site, pCRP can bind to a membrane surface, but only after the membrane has been "activated" by PLA_2 which causes the PC ligands to become extended to be able to fit into the CRP binding pocket. Since all pCRP PC binding sites are located on the same face of the discoid pentamer, multivalent binding energy enables pCRP to be held next to the perturbed membrane surface, drawn close to the apolar zone of the activated membrane. Apolar biochemical forces are now available to weaken the hydrophobic forces holding the CRP pentamer together and keeping the subunit structures tightly compacted. The pCRP molecule begins to "swell", forming an intermediate isoform that has been described as both a

membrane-mCRP ($mCRP_m$) (Ji *et al*. 2007) and a $pCRP^*$ (*i.e.,* pCRP-star) protein (Braig *et al*. 2017). When sufficient biochemical energy is achieved to effectively separate subunits, pCRP undergoes a full structural conversion into mCRP, which now expresses its unique structural, binding, immunogenic and functional properties (Wu *et al*. 2015). Indeed, electron micrographs directly comparing pCRP and mCRP show that mCRP no longer appears as a pentameric disc, but as elongated short, fat fibrils that can self-aggregate into large multimers (Potempa *et al*. 2015). Formation of mCRP from pCRP does not involve a proteolytic cleavage; each protein shares the exact same primary protein sequence. The proteins are conformationally distinctive isoforms which have distinctive antigenicity. While the pCRP antigen is primarily detected and quantified in blood, various studies have reported the mCRP antigen is naturally expressed not in body fluids, but in various tissues, including those involving active inflammatory reactions. By recognizing and carefully controlling the presence and concentrations of each of pCRP and mCRP in experimental systems, it has become clear that mCRP is a potent pro-inflammatory stimulant while pCRP has weak anti-inflammatory activities (summarized in Table 2; Braig *et al*. 2017; McFadyen *et al*. 2018; Potempa *et al*. 2015; Wu *et al*. 2015).

MCRP BINDS CHOLESTEROL

One significant, unique binding ligand now recognized for CRP is cholesterol. The binding site involves a 13-amino acid peptide that is oriented near the PC binding sites of pCRP, extending toward the central void and the inter-subunit contact regions of the pentamer (Fig. 2A). This peptide extends into a hydrophobic cleft of the globular subunit structure, reaching down into the sole intrachain disulfide bond known to be present in the CRP subunit (Ji *et al*. 2009; Li *et al*. 2016). mCRP binding for cholesterol is maximized when the intrachain disulfide bond is reduced, suggesting this mCRP bioactivity may be physiologically regulated by a reduction reaction as might be mediated by thioredoxin or disulfide isomerase (Wang *et al*. 2011). In membranes, mCRP can directly insert into cholesterol-rich lipid rafts (Ji *et al*. 2007, 2009; Wang *et al*. 2011). As lipid raft microdomains are implicated in various receptor medicated cell activation processes involving signaling pathways and nuclear transcription factors (Cheng and Smith 2019), a mechanism by which CRP may regulate inflammation is becoming apparent. Indeed, mCRP has been shown to stimulate intracellular signaling pathways that lead to transcription of pro-inflammatory genes that control the production of the neutrophil chemotactic factor and Interleukin 8 (IL-8), factors known to amplify the acute inflammatory response (Boras *et al*. 2014, 2017; Khreiss *et al*. 2002, 2004a, b, 2005). mCRP binding to lipids is also relevant to lipoproteins metabolism as mCRP has been shown to affects the uptake of low-density lipoproteins (LDLs) by endothelial cells and macrophages (Ji *et al*. 2006; Schwedler *et al*. 2009).

POSSIBLE FUNCTIONAL RELATIONSHIP OF CRP TO GALLBLADDER DISEASE

As the gallbladder is the key storage organ for bile salts and acids, and since bile compounds are synthesized from cholesterol, any compound that binds cholesterol may affect the synthesis and bioactivities of bile. Since gallbladder disease is known to involve significant inflammation in reactions known to be mediated by CRP, interrelationships between CRP, mCRP and cholesterol may be relevant to a better understanding of gallbladder diseases.

While pCRP is known to be synthesized by hepatocytes (Macintyre *et al*. 1983, 1985, 1992), many tissues have been reported to express the human CRP gene and to express a CRP primary protein transcript. As the updates are summarized in the human protein atlas (Thul *et al*. 2018) which describes more than 80% of the human protein-coding genes in 27 organs, the gallbladder is identified as the second ranked organ expressing the CRP gene (Fagerberg *et al*. 2014, updated on 2-Jul.-2019).

In a biodistribution study in normal mice, a small amount of intravenously injected radiolabeled mCRP selective accumulated to the gallbladder (Motie *et al*. 1998). While initially discounted as a relevant event, in light of the newly recognized binding affinity of mCRP for cholesterol and cholesterol analogues, the physiological significance of CRP expression or accumulation in such organs may have important physiological significance.

Of interest, various studies have looked at the effect of statin drugs on CRP levels. Most commonly, studies have looked at how statin treatment, CRP levels and inflammation correlate with disease progression. Since statin drugs target the synthesis of cholesterol, and since the mCRP isoform binds cholesterol and amplifies the acute inflammatory response, studies of statin drug effects and CRP should include an interpretation not only of pCRP blood levels, but of its conversion into mCRP and its interaction with cholesterol. Studies indicate only 20%–64% of patients taking statins

achieve reasonable low-density lipoprotein cholesterol (LDL-C) thresholds (Schleyer *et al*. 2019). The question remains regarding the efficiency of a common current strategy in most medical treatments to restore the biological system to its homeostasis by lowering the elevated of marker(s). While statin therapy in cardiovascular disease is associated with reduction in LDL cholesterol levels, it does not appear to affect CRP levels, including high sensitive CRP levels (hsCRP). Diagnosticians are cautioned not to overinterpret a 50% reduction in hsCRP levels (*i.e*., from 4 to 2 μg/mL) in assessing disease severity or progression. Further studies evaluating the interrelationships of CRP levels, hsCRP levels, cholesterol levels and LDL levels in relation to diseases and associated inflammation levels are warranted.

RECOMMENDED TREATMENTS FOR GALLBLADDER DISEASES

Once confirmation of an acute cholecystitis is obtained, treatment is promptly initiated. Treatment paths differ by operative risk and severity grade. However, a typical course includes withholding oral intake, administering intravenous (IV) fluids and antibiotics, and pain management. The definitive therapy for acute cholecystitis is either early laporascopic cholecystectomy or delayed laparoscopic cholecystectomy, potentially with urgent or early gallbladder drainage prior to surgical removal.

Stable patients with no evidence of perforation or gangrene and no organ dysfunction and mild inflammatory changes are classified as mild (grade I) severity (Yokoe *et al*. 2018). In addition to supportive care, these patients are typically treated with oral antibiotic therapy with coverage against microorganisms in the *Enterobacteriaceae* family, with or without additional anaerobic organism coverage (Gomi *et al*. 2018). Early laparoscopic cholecystectomy is the preferred treatment course in patients with mild disease unless elevated surgical risk precludes this strategy.

Patients with acute cholecystitis accompanied with any one of the following: elevated white blood cell count (>18,000 μL), palpable tender mass in the right upper abdominal quadrant, duration of complaints >72 h, and marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis), are classified as moderate (grade II) severity (Yokoe *et al*. 2018). Patients in this grade severity are treated with IV antibiotics in addition to supportive care. Early cholecystectomy is preferred, but these patients may need to their procedure delayed due to operative risk, and in this case gallbladder drainage may be used to facilitate medical stabilization prior to a delayed cholecystectomy (Okamoto *et al*. 2018).

Patients with organ dysfunction in at least any one of the following: hypotension requiring treatment with dopamine $\geq$ 5 μg/(kg·min), or any dose of norepinephrine, decreased level of consciousness, PaO_2/FiO_2 ratio $<$ 300, oliguria, creatinine $>$ 2.0 mg/dL, INR $>$ 1.5, or platelet count $<$ 100,000 cells/μL, and/or severe local inflammation are classified as severe (grade III) severity (Yokoe *et al*. 2018). Patients in this category are treated with IV antibiotics as well as are referred for urgent management of severe local inflammation by early cholecystectomy or percutaneous gallbladder drainage (*i.e*., percutaneous cholecystostomy tube) followed where indicated by delayed cholecystectomy at least 6 weeks later, when the patient's general condition has improved (Okamoto *et al*. 2018).

DISCUSSION

Inflammation is the innate immune response to potentially harmful stimuli such as pathogens, injury, cancers and metabolic stress. The ultimate and essential function the naturally stimulated host defense inflammatory response is to rapidly react to and control any threats to survival and to restore the optimal homeostatic state.

When the acutely activated inflammatory response incompletely or inefficiently coordinates host defenses and restores healthful homeostasis, a muted response can persist, leading to a chronic condition that can be deleterious to the individual. Chronic inflammation can damage rather than protect and repair tissues by continuing to produce and secrete non-specific oxidizers (*e.g*., peroxide and peroxynitrite) and degrative enzymes (*e.g*., proteases, hydrolases) which indiscriminately continue to attack both disease-associated and normal tissues involved in the host defense response. Various vasoactive substances continue to be generated, as are cytokine mediators and neuropathic substances which cause continued tissue damage and pain. Chronic inflammation can lead to continued and progressive tissue damage which can, over time, contribute to the exacerbation of diseases that can become life threatening. While acute inflammation is vital to survival and an aggressive host defense against threats to health, chronic inflammation is pathological and problematic to good health (Antonelli and Kushner 2017; Chen *et al*. 2018).

CRP is widely understood as a blood diagnostic marker whose blood levels change rapidly correlate with active inflammatory processes. While its quantified

presence correlates with inflammation, its role contributing to or regulating such processes had remained unknown even with decades of study. With the recent discovery that CRP can change structure into a distinctive isoform with distinctive solubility, antigenicity and binding activities, the biofunction of CRP as a modulator of inflammation is emerging. The widely recognized, serum-soluble pentameric CRP (pCRP) can bind structures presenting phosphorylcholine moieties, activate the classis complement pathway and act as an opsonin for leukocyte phagocytosis. Its overall biofunction, however, is now recognized being anti-inflammatory. When pCRP is converted into mCRP, however, it expresses cholesterol binding activity and can insert into lipid rafts where it activates many pathways that amplify the acute inflammatory response. mCRP is known to promote chemotaxis and recruitment of circulating leukocytes to areas of inflammation and to delay apoptosis. mCRP increases IL-8 and MCP-1 production and to affect the uptake of oxidized LDL. Most notably, mCRP is strongly pro-inflammatory. When it is produced at local sites of tissue damage, it, rather than the pCRP molecule, is the prototypic acute phase reactant, amplifying acute inflammatory responses (Sproston and Ashworth 2018; Wu *et al*. 2015). Acute inflammation can be healthful and protective and may be a preferred response to threats to tissue integrity and function. As the understanding of how and where mCRP is produced in tissues involved in both health and disease, the true role of CRP in reactions of inflammation will finally be established.

The gallbladder is an important component of the hepatobiliary system whose primary function is to aid in digestion of foodstuffs and facilitate removal of waste products from the body into the intestine. The gallbladder is principally a storage organ for bile—chemically modified salts and acids of cholesterol which are synthesized in the liver and which function as surfactants to solubilize lipids and other fatty substances that are introduced into the body. However, since cholesterol has an important role in cellular function, it can also be directly synthesized by each cell in the body (Huff and Jialal 2019). The biochemical nature of fatty substances is to avoid or minimize contact with water. To minimize the energy needed to maintain an interface with the aqueous phase, fatty substances self-associate into aggregates with a non-aqueous core that can form waxy, molecular clumps of various size. Bile is a natural detergent molecule that functions by sitting on the surface of fatty aggregates, lowering the energy barriers needed to maintain an interface with water and limiting the size of any apolar clumps. By limiting particle size and establishing an aqueous interface, bile facilitates the movement of bile-coated lipids through the digestive system.

The structure of the hepatobiliary system (*i.e*., the hepatobiliary tree) includes the liver as a source of bile, the cystic duct which carries bile from the liver to the gallbladder, the gallbladder itself which is the primary storage and concentrating organ for bile, the common biliary duct that carries bile through the pancreas (where digestive enzymes can be introduced into processed foodstuffs), and the duodenum (*i.e.,* the first part of the small intestine) where compounds moving through this tree are deposited. As the hepatobiliary system is designed to help process poorly- or non-soluble lipidic masses, any defect in the biochemistry of how bile is formed, stored, transported, or how it successfully functions to disaggregate fatty clumps, can lead to unhealthful accumulation of these clumps which can congest the proper flow of materials through the hepatobiliary tree, and lead to disease. Non-solubilized fatty deposits can grow into and form gallstones, a hallmark structures of gallbladder diseases. Gallstones can obstruct any part of the biliary tree and in turn introduce structural stress into the system anatomy, leading to damaged tissues. When any tissue become damaged, no matter what the cause, the body reacts to the introduced threat to health and homeostasis by activating natural host defense responses which includes inflammation.

The initial host defense response to tissue damage includes immediate and aggressive activation of inflammation that stimulates vasoactive and cellular responses focused on controlling the threat, attacking and removing any foreign material, and restoring healthful tissue structure and function. Inflammation is non-specific to the inciting cause initiating the response; its destructive responses (*e.g*., generation of reactive oxygen species and degradative enzymes) will affect near-by normal tissues. Inflammation that persists over long times (*i.e*., chronic inflammation) can adversely compromise normal tissue structures and functions and contribute to many symptoms and pathologies associated with continued, prolonged disease.

Gallbladder disease that involves inflammation is known as Cholecystitis. In diagnosing diseases of the gallbladder, consideration should be given to whether disease is caused by obstructions, whether disease involves tissue damage caused by obstruction or some other factor, the extent of any tissue damage, and whether there are confounding contributions of infections or cancers in affected tissues. In severe cases of cholecystitis, a cholecystectomy, *i.e*., the surgical removal of the gallbladder and other involved tissues, remains the mainstay of treatment.

In gallbladder diseases, significantly elevated CRP levels correlate with diagnosis of acute cholecystitis and may be of value in differentiating chronic cholecystitis and gallbladder cancer. Using well defined elevated CRP levels in conjunction with ultrasound exams and white blood cell counts, CRP can be used to enhance the diagnosis of acute cholecystitis. CRP levels have been used to predict the outcome and prognosis of gallbladder resection in gallbladder cancer, and to predict acute cholecystitis severity. Also, the short-term changes of CRP levels in blood (*i.e.*, 6–10 h), is suggesting the needs of more frequent testing/a profile testing especially throughout the complication evaluation to better understanding the CRP turnover during its 19 h half-life. For example, to achieve 95% confidence (0.95 probability) 14 samples per period concluded to be required to characterize the CRP levels. (Dorraki *et al*. 2018).

As an understanding of CRP structural isoforms is evolving, CRP should now be evaluated not only as a marker for gallbladder disease, but as a modulator of natural defense mechanisms that are activated in response to disease pathologies. The functional interrelationships of CRP and its different isoforms as natural mediators of gallbladder disease pathophysiology is entering a new era.

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Compliance with Ethical Standards

Conflict of interest Ibraheem M. Rajab, Daniel Majerczyk, Margaret E. Olson, Jenna M.B. Addams, Mihee L. Choe, Matthew S. Nelson and Lawrence A. Potempa declare that they have no conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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