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MINI-REVIEW

Allosteric regulation of C-reactive protein

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Abstract Serum-soluble C-reactive protein (CRP) is a highly conserved innate immune pattern recognition molecule comprised of five identical globular subunits arranged in a cyclic pentameric shape. While the interactions between each of the five subunits are noncovalent, each monomer possesses an intra-subunit disulfide bond linking adjacent β-strands within the same β-sheet (*i.e.*, a cross-strand disulfide bond). This bond is necessary for the folding and polymerization of CRP during its synthesis, but also serves as a regulator of CRP function. Reduction of the bond initiates a conformational, allosteric change that exposes a hidden binding site for cholesterol and amplifies CRP-mediated cellular responses. In this review, we discuss the folding, multimerization, and structural changes CRP undergoes during its life cycle. We also highlight the role of the cross-strand disulfide bond in CRP, both for its contributions to the assembly of the pentamer and for its role as an allosteric regulator of CRP function.

Keywords CRP, Allosteric, Disulfide bond, Pentraxin, Protein conformation

INTRODUCTION

For some time, C-reactive protein (CRP) was mistakenly assumed to be a structurally inflexible protein with only one biologically relevant isoform (Pepys and Hirschfield 2003). This argument had support from crystallographic analysis of ligand-bound CRP, whose quaternary structure was nearly identical to its ligand-unbound form (Shrive *et al.* 1996; Thompson *et al.* 1999). However, this structure was generated from a soluble version of CRP bound to similarly soluble ligands. These conditions were necessary for its crystallization, but they did not reflect the membranous conditions in which CRP binds its primary ligands. Further investigations would determine that CRP does have structurally and antigenically distinct isoforms (Braig *et al.* 2014; Ji *et al.* 2007; Olson *et al.* 2023; Potempa *et al.* 1983, 1987, 2025; Rajab *et al.* 2020a, b; Thiele *et al.* 2014; Wu *et al.* 2015), with membrane-association being a critical factor in initiating those changes (Alnaas *et al.* 2017; Rajab *et al.* 2020b; Wang and Sui 2001; Wang *et al.* 2012). Importantly, the recognition of multiple different biologically relevant isoforms also provided an explanation for a long-time mystery associated with CRP – the contradictory reports of CRP mediating pro- and anti-inflammatory effects (Potempa *et al.* 2025). Current understanding now has it that the serum-soluble pentameric CRP (pCRP), the molecule's native state, is non-inflammatory or weakly anti-inflammatory. Conversely, two alternative isoforms of CRP were responsible for eliciting potent immune responses, these being a "relaxed" membrane-associated pentamer called pCRP* (Braig *et al.* 2017; Ji *et al.* 2007; Lv and Wang 2018;

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Miyazawa *et al.* 1988) and a principally membrane-embedded monomer (mCRP) formed after the pentamer irreversibly dissociates (Cheng *et al*. 2022; Kresl *et al*. 1998; Potempa *et al*. 1983, 1987).

While consensus now recognizes the existence of multiple biologically relevant CRP isoforms, the detailed processes by which pCRP relaxes and dissociates into its pro-inflammatory states are still being fully elucidated. As aforementioned, ligand recognition by itself is not sufficient to cause structural changes (Noone *et al.* 2021; Potempa *et al.* 1987; Shrive *et al.* 1996; Thompson *et al.* 1999). Rather, ligands must be provided as an array and/or on lipid membranes with high curvature (Agrawal *et al.* 2001; Alnaas *et al.* 2017; Rajab *et al.* 2020b; Wang and Sui 2001; Wang *et al.* 2012). Acidic microenvironmental conditions like those generated during acute inflammatory responses also contribute to structural rearrangements (Erra Díaz *et al.* 2018; Hammond *et al.* 2010; Li *et al.* 2018; Noone *et al.* 2021), as well as other local effector molecules such as reactive oxygen species (ROS) (Boncler *et al.* 2018; Li *et al.* 2018). Evidence additionally suggests an important role for the cross-strand disulfide bond within each CRP monomer in regulating CRP structure and function (Jia *et al.* 2018; Li *et al.* 2016, 2018; Wang *et al.* 2011). In this review, we discuss the folding, multimerization, and structural changes CRP undergoes during its life cycle. We also highlight the dual role of the cross-strand disulfide bond in CRP: its contributions to the assembly of the pentamer and its importance to CRP-associated functional responses.

STRUCTURE OF THE CRP MONOMER

Each subunit of CRP is a non-glycosylated globular protein of 206 amino acids and 23 kDa mass (Shrive *et al.* 1996). The major structural feature is a hydrophobic core mainly comprised of two 4-stranded β-sheets arranged in a jelly roll fold (Fig. 1A) (Thompson *et al.* 1999). The β-sheets are highly evolutionarily conserved, containing numerous aromatic amino acids and a pair of cysteines (Pathak and Agrawal 2019; Zhou *et al.* 2024). In human CRP, the cysteine residues (C36 and C97) are in adjacent strands of the same 4-stranded β-sheet and form a cross-strand disulfide bond (Guillon *et al.* 2014; Mikolajek *et al.* 2011; Noone *et al.* 2021; Ramadan *et al.* 2002; Shrive *et al.* 1996; Thompson *et al.* 1999; Zeller *et al.* 2023). From a three-dimensional perspective, the disulfide is bordered laterally by a pair of tryptophans (W110 and W162; Fig. 1B), which are important to the stability of the hydrophobic core and ostensibly also protect the disulfide bond from nucleophilic or oxidative attack under neutral conditions (Bhattacharyya *et al.* 2004; Ioerger *et al.* 1999; Wang *et al.* 2011). Also immediately adjacent to the disulfide bond are the only two histidine residues in CRP (H38 and H95). The imidazole ring of H95 is angled toward the disulfide bond, while the ring of H38 forms a stacking interaction with a tryptophan near CRP's C-terminus (W205) (Thompson *et al.* 1999). Very little of the CRP secondary structure is helical (<5%), with the only α-helix to complete two full turns located immediately above the disulfide bond. On the face opposite of this helix are the calcium-binding sites, where residues D60, N61, E138, D140, and Q150 coordinate a pair of Ca^{2+} ions necessary for CRP to interact with its primary ligand of phosphocholine (Agrawal *et al.* 1992; Lee *et al.* 2002; Thompson *et al.* 1999).

Nascent CRP monomers fold into this initial conformation in a two-stage process (Lv *et al.* 2018, 2020). The first stage is a spontaneous process in which most β-strands in the jelly roll fold self-assemble (Lv *et al.* 2018). A dipeptide (L29-P30) that is slightly N-terminal of the first β-strand in this fold is absolutely required for this process (Lv *et al.* 2020), with the proline likely serving as a cap to the structural element. The major α-helix also spontaneously organizes and locates to its position above the cysteines. Its presence, and specifically I171, is required for disulfide bond formation (Lv *et al.* 2020). The prerequisite for I171 likely reflects a need for its R-group to orient the amino acid adjacent to C97 (*i.e.*, T98) into a position that favors continuation of the β-strand; in the absence of I171, T98 might otherwise be a strand-terminating residue. The formation of the disulfide bond marks the end of the spontaneous phase of folding, because the second phase of CRP's folding process requires the disulfide bond to be in place to preserve the central core (Cheng *et al.* 2022; Lv *et al.* 2018).

In this second phase, the major action is the incorporation of the remaining β-strands of the jelly roll fold (Lv *et al.* 2018). Though unnecessary for the spontaneous phase of folding, calcium occupying its two binding sites on CRP increases the efficiency with which the non-spontaneous remodeling activities take place (Lv *et al.* 2018). Those binding sites are located within the loop connecting the β-strands incorporated into the structure during the second phase of folding (Lv *et al.* 2018; Shrive *et al.* 1996).

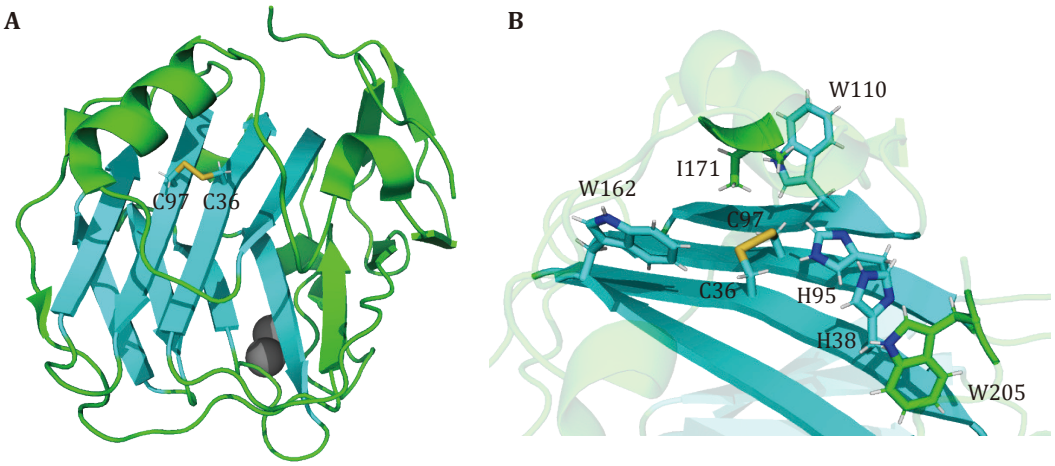

Fig. 1 Structure of a folded CRP monomer (PDB ID, 7PKB). **A** Overview of the CRP monomer with the disulfide bond (yellow) and jelly roll fold (cyan) in view. Two calcium ions (grey) are positioned on the far side of the monomer. **B** Select residues nearby the disulfide bond important to its formation and stability. CRP, C-reactive protein; PDB, protein data bank

FORMATION OF THE SERUM-SOLUBLE CRP PENTAMER

After the disulfide bond has formed, five CRP monomers can assemble into a cyclic pentamer with radial symmetry (Chakraborty and Agrawal 2013; Cheng *et al.* 2022; Lv *et al.* 2018, 2020; Thompson *et al.* 1999). All subunits of the CRP pentamer are oriented in the same direction, yielding a relatively planar oligomer with two distinct faces (Fig. 2) (Noone *et al.* 2021; Thompson *et al.* 1999). These are typically referred to as the binding face (B-face) and the effector or activating face (A-face). The B-face includes the calcium-binding site and primarily interacts with exposed phosphocholine headgroups (Agrawal *et al.* 1992; Lee *et al.* 2002; Thompson *et al.* 1999); the A-face interacts with functional partners such as complement protein C1q and Fc receptors (Agrawal *et al.* 2001; Bang *et al.* 2005; Thompson *et al.* 1999). Interactions with C1q initiate the classical complement pathway, though generally only resulting in opsonization and phagocytosis of CRP-bound targets without activation of the membrane attack complex (Haapasalo and Meri 2019). Functional effects downstream of Fc receptors are extensive and vary by cell type. For example, CRP-Fc receptor interactions enhance neutrophil survival and nitric oxide production, as well as promoting monocyte differentiation into pro-inflammatory M1 type macrophages (Potempa *et al.* 2025).

Pentamer integrity is maintained by three major features. Foremost among them are a trio of salt bridges formed between each subunit pair: E101–K201', K123–E197' and R118–D155' (Fig. 2B) (Lv *et al.* 2018, 2020; Thompson *et al.* 1999). Disrupting any of these interactions reduces the efficiency of pCRP secretion, though the R118–D155' bridge is of particular importance because its loss completely abrogates pCRP release (Lv *et al.* 2018, 2020). The R118–D155' salt bridge is distinct from the others in that it is completely buried in the interface between subunits, and is additionally noteworthy for utilizing a more uncommon non-planar/monodentate configuration (vs more energetically favorable planar/bidentate configurations) (Donald *et al.* 2011; Potempa *et al.* 2022). Second, calcium binding to the B-face also provides important stability to the pentamer, as evidenced by impaired secretion of CRP following mutation of the calcium-binding site, calcium-dependent resistance to denaturation in high concentrations of urea, and calcium-dependent resistance to proteolysis (Cheng *et al.* 2022; Lv *et al.* 2018; Okemefuna *et al.* 2010; Potempa *et al.* 1983; Thompson *et al.* 1999; Ying *et al.* 1992; Zhang *et al.* 2020). This protective effect likely stems from tighter packing of the monomers together, given that the apparent size of the pentamer increases following chelation of the calcium ions (Rajab *et al.* 2020a). And lastly, the intra-subunit disulfide bonds provide thermodynamic stability to pCRP, helping to extend its half-life while in circulation (Hogg 2003).

CONFORMATIONAL REMODELING OF PENTAMERIC CRP AND DISSOCIATION INTO mCRP

Before dissociation of pCRP into mCRP was demonstrated *in vivo* (Thiele *et al.* 2014), there was ample *in vitro*

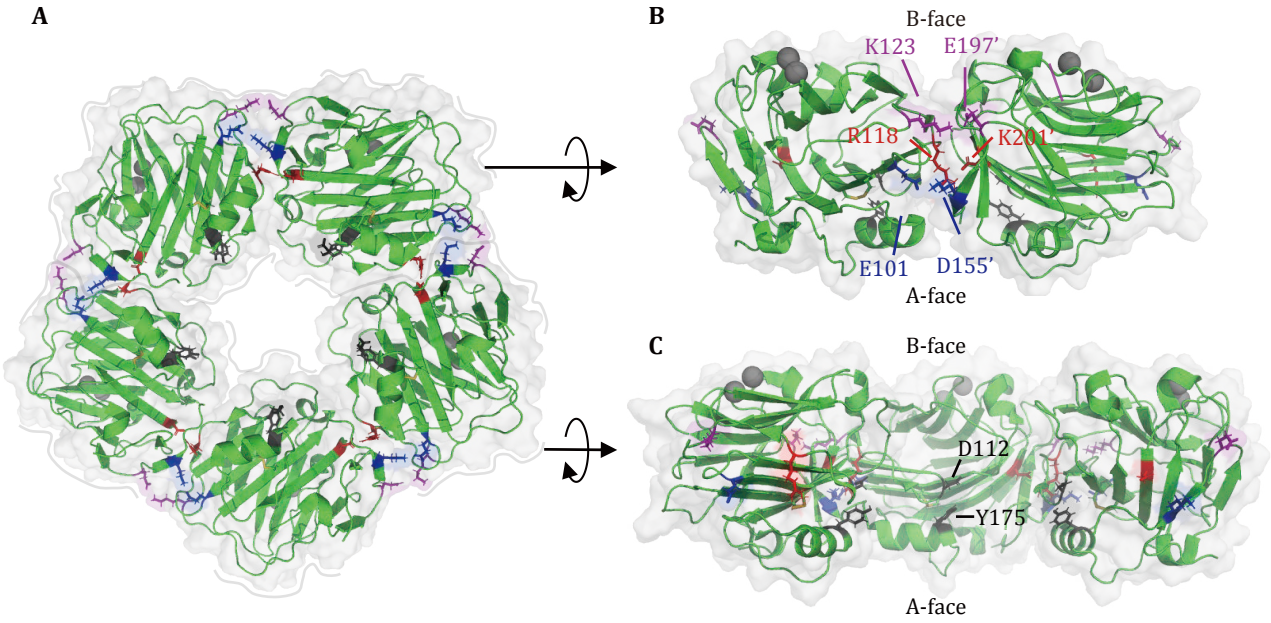

Fig. 2 Structure of the serum-soluble CRP pentamer (PDB ID, 7PKB). **A** Overview of the pentameric quaternary structure with the disulfide bonds (yellow) in view. Also shown are residue pairs taking part in the salt bridges critical to pentamer stability (red, blue, purple), residues important to CRP interactions with complement component C1q (dark grey), and calcium ions (light grey). **B** Alternative view of the salt bridges mediating the interaction between subunits of the pentamer. Only two subunits are shown. **C** Alternative view showing the positioning of two residues important for contacts with C1q relative to the A-face of the CRP pentamer. Only three subunits are shown. A-face, activating face; B-face, binding face; CRP, C-reactive protein; PDB, protein data bank

data to suggest the individual subunits of CRP had more pro-inflammatory potential than the pentameric isoform (de la Torre *et al.* 2013; Eisenhardt *et al.* 2012; Fujita *et al.* 2014; Khreiss *et al.* 2002, 2004a, 2004b, 2005; Miyazawa *et al.* 1988; Molins *et al.* 2008, 2011; Potempa *et al.* 1988; Zouki *et al.* 2001). However, as aforementioned, these data conflicted with the rigidity implied by the similarity between the ligand-bound and ligand-unbound structures of serum-soluble CRP (Shrive *et al.* 1996; Thompson *et al.* 1999). Because only pCRP had been detected *in vivo*, the field initially favored the more static concept of CRP; nevertheless, evidence began accruing to challenge that view. For example, a mutational analysis looking for residues important to the interaction between CRP and complement protein C1q identified D112 and Y175 as contact points (Agrawal *et al.* 2001). Both residues are in the central cleft of the CRP pentamer (Fig. 2C), indicating that CRP subunits may need to tilt or rotate to fully expose the C1q binding site. Additionally, studies utilizing intrinsic tryptophan fluorescence spectroscopy and ANS (8-anilino-1-napthalenesulfonic acid) found alterations in the fluorescence profile of CRP consistent with a two-phase conformational remodeling process (Ji *et al.* 2007; Miyazawa *et al.* 1988; Wang *et al.* 2011). In other words, these data suggested pCRP temporarily assumes an altered pentameric conformation before irreversibly dissociating into individual monomers. Ultimately, CRP displaying epitopes specifically associated with mCRP were observed in a rat model of myocardial infarction, in inflamed human tissues, and on extracellular vesicles in human serum, putting to rest the question of whether non-native CRP forms exist *in vivo* (Braig *et al.* 2014; Crawford *et al.* 2016; Eisenhardt *et al.* 2009; Fujita *et al.* 2022; Habersberger *et al.* 2012; Molins *et al.* 2011; Thiele *et al.* 2014; Zhang *et al.* 2018). The key hurdles to detecting mCRP were that its extreme insolubility confines it to membranes and the uncertainty of its half-life. Others then also confirmed the presence of the altered pentameric form (Braig *et al.* 2017; Lv and Wang 2018), validating the models proposed by the mutational analysis and fluorescence spectroscopy data.

While pCRP* and mCRP are now known to be biologically relevant, the requirements for their emergence *in vivo* remain an active area of investigation. As prefaced, ligand binding by itself is insufficient to induce substantial structural changes (Noone *et al.* 2021; Thompson *et al.* 1999). This is true both at neutral pH and acidic pH (pH 5) (Noone *et al.* 2021), the latter being more representative of the inflammatory microenvironments in which CRP acts (Erra Díaz *et al.* 2018;

Kato *et al.* 2013). Instead, the major driver of conformational change appears to be the curvature of the membrane displaying CRP ligands (Alnaas *et al.* 2017; Rajab *et al.* 2020b; Wang *et al.* 2012). These ligands, the primary example being phosphocholine, are usually inaccessible until modified by reactive oxygen species (ROS) or enzymes like phospholipase A2 (Caprio *et al.* 2018; Greenberg *et al.* 2008). The modification gives the lipids a detergent-like effect that disrupts membrane packing and causes localized changes in membrane shape and lipid organization (McMahon and Gallop 2005; Megli and Russo 2008; Plochberger *et al.* 2010). Ostensibly, the higher curvature of these regions could force CRP subunits to adjust their positioning to accommodate the non-standard spatial organization of their ligands. Additionally, the increased curvature may expose hydrophobic regions of the membrane, which can induce structural changes by competing for the apolar interactions stabilizing folded pCRP subunits (Alnaas *et al.* 2017; Rajab *et al.* 2020b).

Though not the primary drivers of CRP remodeling, other microenvironmental factors provide key contributory roles. For example, the major exception to an otherwise limited effect of low pH on pCRP structure is the disruption of the K123–E197' salt bridge (Noone *et al.* 2021). This is sufficient to alter the flexibility between subunits and decrease the overall stability of the pentamer (Noone *et al.* 2021), as shown by the reduction in CRP secretion when the interaction was intentionally removed (Lv *et al.* 2020). The histidine residues in each CRP subunit are also protonated under low pH conditions, which impacts CRP subunit flexibility by changing the hydrogen bonding network (Noone *et al.* 2021). Immunologic effector molecules produced during an inflammatory response also affect CRP structure, as exemplified by ROS, which can loosen CRP's pentameric structure and unmask hidden hydrophobic functional regions (Boncler *et al.* 2018; Li *et al.* 2018; Singh *et al.* 2017). In summary, local environmental conditions help promote a more relaxed and flexible CRP structure. These changes facilitate their interactions with membrane lipids, as well as promote the exchange of hydrophobic interactions that occur when CRP dissociates into the membrane.

AN ALLOSTERIC DISULFIDE BOND IN CRP

Disulfide bonds can be categorized according to the geometry of the five χ angles associated with the bond (Fig. 3A) (Chiu and Hogg 2019; Cook and Hogg 2013; Schmidt *et al.* 2006; Schmidt and Hogg 2007). There are three general conformations, hooks, spirals, and staples, that are further subdivided into right- or left-handed groups with a plus, minus, or +/– designation based on whether certain χ angles have positive or negative values. For example, the disulfides in pCRP meet the criteria for the group labeled minus right-handed (–RH) staples (Fig. 3B) (Cook and Hogg 2013). Particularly notable about the –RH staples group is that it represents the archetypal allosteric disulfide bond (Chiu and Hogg 2019; Schmidt *et al.* 2006). These types

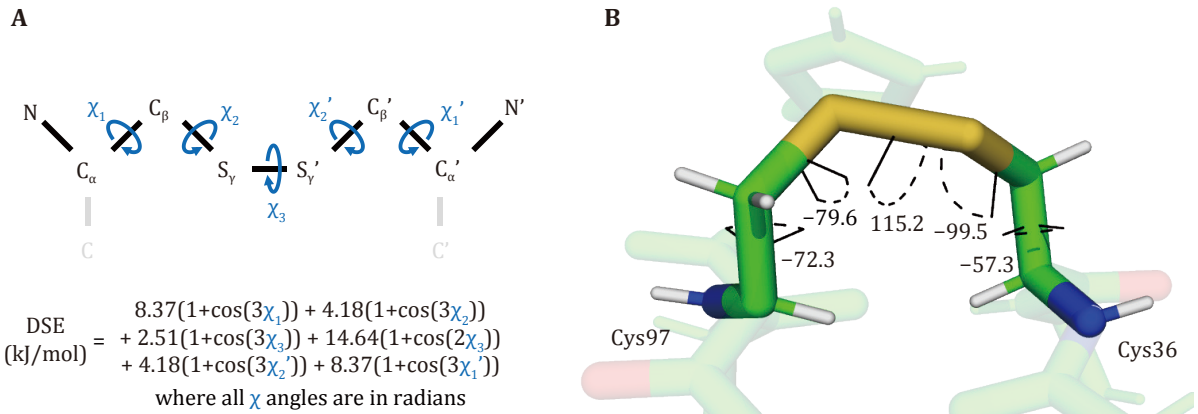

Fig. 3 CRP disulfide bond geometry. **A** Diagram depicting the χ angles of a disulfide bond. Calculation of each χ angle includes the four nearest atoms to the label that are in black text (*e.g.*, χ_1 is calculated using N, C_α, C_β, and S_γ). Also shown is the formula for approximating the DSE of a disulfide bond based on the χ angles (Schmidt *et al.* 2006). **B** Example of a –RH staple disulfide bond found within a CRP subunit (PDB ID, 7PKB). Values for the χ angles were calculated using the dihedrals measurement tool in PyMOL (Version 3.1.5.1; Schrödinger, LLC) and are shown in degrees. CRP, C-reactive protein; DSE, dihedral strain energy; PDB, protein data bank; –RH, minus right-handed

of disulfide bonds, in contrast to inert disulfide bonds with purely structural roles or catalytic disulfides that regulate other protein functions, have a regulatory role in controlling their own protein's function (Chiu and Hogg 2019; Cook and Hogg 2013). A general example of this regulation would be altering the set of a protein's binding partners based on whether the allosteric disulfide bond is intact or reduced.

One major reason −RH staples are frequent examples of allosteric disulfide bonds is because they have a large amount of inherent torsional stress that makes them more susceptible to cleavage (Chiu and Hogg 2019; Pijning *et al.* 2018; Zhou *et al.* 2014). That stress can be illustrated through a calculation of the bond's dihedral strain energy (DSE) (Schmidt *et al.* 2006). Whereas the most common type of disulfide bond (*i.e.*, the archetypal structural disulfide) has an average DSE of 10.1 (95% CI, 9.7–10.4) kJ/mol, −RH staples have an average of 18.1 (17.3–18.8) kJ/mol (Schmidt *et al.* 2006; Schmidt and Hogg 2007). Notably, the apparent stress in CRP's disulfide is above even the average for −RH staples, with the mean DSE calculated from 14 available crystal structures of human CRP equaling 21.0 (20.6–21.5) kJ/mol (Table 1; https://services.mbi.ucla.edu/disulfide/). Moreover, these estimations are based on frozen crystallized proteins, which generally possess lower strain energy compared with proteins in-solution (Schmidt and Hogg 2007).

These observations suggest that the disulfide bond in CRP could be an allosteric regulator of CRP functions (Cook and Hogg 2013). Indeed, direct comparisons of cellular responses following treatment with reduced or non-reduced mCRP found reduced mCRP to be up to 40-fold more potent (Li *et al.* 2016; Wang *et al.* 2011), implying that considerable functionality is locked behind the disulfide bond. Moreover, the oxidation state of the disulfide in CRP likely regulates the ligands with which CRP interacts. One of the neoepitopes exposed in

Table 1 Dihedral strain energies of −RH staple bonds in human CRP relative to other disulfide bond configurations

	Number	DSE (95% CI), kJ/mol		REF
All disulfides	42690	13.1 (13.1–13.2)		Schmidt and Hogg 2007
−LH spirals only	12684	10.5 (10.4–10.6)		
−RH staples only	3641	17.7 (17.5–17.9)		
CRP (overall)	159[a]	21.0 (20.6–21.5)[b]		–
PDB ID[c]	Number	Ligand	DSE (range), kJ/mol	PDB REF
1B09	5	PC	25.8 (23.1–29.2)	Thompson *et al.* 1999
1GNH	10	None	21.0 (20.1–22.0)	Shrive *et al.* 1996
1LJ7	10	None	25.0 (24.4–26.1)	Ramadan *et al.* 2002
3L2Y	20	PE	17.8 (15.9–20.3)	Mikolajek *et al.* 2011
3PVN	20	None	17.9 (14.1–19.8)	Guillon *et al.* 2014
3PVO	20	None	22.4 (19.8–26.0)	Guillon *et al.* 2014
7PK9[d]	10	None	20.1 (18.6–20.9)	Noone *et al.* 2021
7PKB[d]	5	None	20.8 (20.2–21.8)	Noone *et al.* 2021
7PKD[d]	10	PC	21.3 (19.9–23.2)	Noone *et al.* 2021
7PKE[d]	5	PC	20.5 (20.4–20.7)	Noone *et al.* 2021
7PKF[d,e]	10	None	20.6 (19.7–22.0)	Noone *et al.* 2021
7PKG[d,e]	5	None	20.3 (20.2–20.6)	Noone *et al.* 2021
7PKH[d,e]	9[a]	PC	20.6 (19.0–22.4)	Noone *et al.* 2021
7TBA	20	PC Mimetic	24.3 (23.0–25.9)	Zeller *et al.* 2023

CRP, C-reactive protein; DSE, dihedral strain energy; −LH, minus left-handed; PC, phosphocholine; PE, phosphoethanolamine; −RH, minus right-handed.
[a]One disulfide bond presented as a −/+ right-handed hook with a DSE of 20.9 kJ/mol. Though this conformation is still associated with allosteric disulfides (Chiu and Hogg 2019), it was omitted from the analysis.
[b]Values for χ angles were acquired using the dihedrals measurement tool in PyMOL (Version 3.1.5.1; Schrödinger, LLC), converted to radians, and entered into the formula shown in Fig. 3A to estimate each bond's DSE. Calculated values were checked against results provided from the online resource at https://services.mbi.ucla.edu/disulfide/ and were in agreement to the tenths place.
[c]Unless otherwise indicated, CRP structures were generated in neutral pH conditions and by X-ray diffraction.
[d]Structure generated by electron microscopy.
[e]Crystallized in acidic (pH 5) conditions.

mCRP is a stretch of amino acids important for membrane insertion due to its ability to directly interact with cholesterol (Ji *et al.* 2009; Li *et al.* 2016). This sequence, V_{35}CLHFYTELSSTR$_{47}$, contains one of the cysteines involved in the disulfide bond. Moreover, a peptide corresponding to this region blocks cellular responses to mCRP, demonstrating the importance of the sequence in mediating mCRP-associated functions (Li *et al.* 2016). Altogether, these observations imply that the reduction of the disulfide bond is necessary for the full spectrum of CRP functional responses, and therefore that the disulfide bond in CRP is an allosteric regulator of CRP activities.

REDUCING THE DISULFIDE BOND IN CRP

The most likely mechanism by which the disulfide bond in CRP could be severed is via the actions of an oxidoreductase (Chiu and Hogg 2019; Cook and Hogg 2013). While CRP has a more extensive role in an inflammatory response than simply the immediate acute phase (Potempa *et al.* 2025), candidate oxidoreductases would likely still be present at the earliest point in which its effects are evident. For tissue damage, this would be during hemostasis as CRP has a well-known role in promoting platelet activation and aggregation (Boncler *et al.* 2011, 2018; de la Torre *et al.* 2013; Miyazawa *et al.* 1988; Molins *et al.* 2011). Moreover, the membrane blebbing that occurs during platelet activation presents membrane conditions highly favorable for structural remodeling of the CRP pentamer (Eisenhardt *et al.* 2009; Scridon 2022). Platelets express several oxidoreductases important for normal clot formation, including enzymes like protein disulfide-isomerase, endoplasmic reticulum protein (ERp)5, ERp57, thioredoxin-related transmembrane protein (TMX)1, and TMX3 (Cho *et al.* 2008; Holbrook *et al.* 2010, 2012; Jordan *et al.* 2005; Lv *et al.* 2024). Unfortunately, no study to date has examined whether these specific oxidoreductases can cleave the disulfide bond in CRP. However, reduction of the bond in CRP by thioredoxin has been demonstrated *in vitro* (Wang *et al.* 2011), suggesting that the thioredoxin-related proteins could be strong candidates. Thioredoxin itself may also provide the means of breaking CRP disulfides in some scenarios, as implied by the colocalization of thioredoxin with mCRP in human coronary artery plaques (Wang *et al.* 2011).

Alternatively, the initial structural changes in CRP at regions of high membrane curvature could mechanically stretch and rotate the disulfide bonds to the extent that they become susceptible to hydrolysis. Crystal structures of pCRP have detected a conserved water molecule positioned immediately adjacent to the disulfide bond (Guillon *et al.* 2014; Mikolajek *et al.* 2011; Noone *et al.* 2021), consistent with this possibility. However, hydrolytic cleavage of disulfide bonds typically occurs in alkaline conditions (Hogg 2003). Acid-base assisted hydrolysis is also a possibility (Hogg 2003), though the carboxylate anion that would initiate the process is not immediately apparent. Regardless, there is proof of concept for hydrolytic cleavage of a disulfide bond in an artificially engineered metalloprotein (Churchfield *et al.* 2016). In that example, the disulfide bond underwent hydrolysis after chelation of its Zn^{2+} ions. Little is known of the fate of the CRP's calcium ions during or after dissociation into mCRP *in vivo*, but its absence does facilitate mCRP formation *in vitro* (Potempa *et al.* 1983, 1987; Ying *et al.* 1992; Zhang *et al.* 2020). Thus, the possibility of calcium sequestration enabling strain-facilitated hydrolysis of the CRP disulfide bond merits investigation.

SUMMARY AND PERSPECTIVES

Newly synthesized CRP monomers undergo a spontaneous folding process culminating in the formation of a cross-strand disulfide bond packed with a large amount of torsional stress. This bond is necessary for a second non-spontaneous set of events that completes assembly of the monomer's central jelly roll fold, as well as for the formation of salt bridges linking five subunits together into a pentamer. CRP retains this shape until it binds ligands on regions of high membrane curvature. There, the spatial orientation of those ligands, combined with the effects of microenvironmental factors like acidic pH and ROS, likely cause the pentamer to relax and the individual subunits to tilt or rotate. These structural changes, alongside the destabilizing effect hydrophobic regions of the membrane have on the interactions holding the hydrophobic core of each subunit together, culminate in the pentamer irreversibly dissociating into individual subunits and those subunits entering the membrane. At some point during this process, the disulfide bond is cleaved, altering the set of ligands with which CRP interacts and enhancing CRP-mediated functional responses. Given the critical role of the disulfide bond in monomer folding and pentamer assembly, we speculate that its reduction is the trigger for pentamer dissociation. The initial structural remodeling of pCRP into pCRP* could grant local oxidoreductases access to the disulfide bond, which is otherwise protected while in the flatter and more compact serum-soluble pCRP conformation. Upon

its cleavage, pentamer stability would be irreversibly compromised, thereby facilitating the exchange of inter-subunit hydrophobic interactions for interactions with alternative ligands such as cholesterol.

Lastly, we note that one of the cysteines in the CRP allosteric disulfide is part of a conserved eight amino acid sequence known as the pentraxin signature sequence (His-X-Cys-X-[Ser/Thr]-Trp-X-Ser, where X is any amino acid) (Wang *et al.* 2020). Intriguingly, CRP is not unique in having its "signature" cysteine take part in a cross-strand disulfide bond. Such a disulfide exists in all pentraxins with an available crystal structure (*i.e.*, serum amyloid P component, pentraxin 3, and neuronal pentraxin 1) (Mikolajek *et al.* 2011; Noone *et al.* 2022; Suzuki *et al.* 2020). While tempting to speculate that the same allosteric mechanism regulating CRP structure and function extends to all pentraxins, more research is necessary before any such conclusions may be made. Regardless, the available data suggests much of CRP's pro-inflammatory potential is locked behind an allosteric disulfide bond. And ultimately, therapeutic agents capable of preventing cleavage of CRP's disulfide bond may provide a fresh avenue for treating a variety of adverse health conditions (Du Clos 2013; Wang *et al.* 2020).

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Compliance with Ethical Standards

Conflict of interest Lawrence A. Potempa is the founder and shareholder of Acphazin, Inc. Marc Potempa is an employee of Acphazin, Inc. Ibraheem M. Rajab is an employee of Tabuk Pharmaceuticals. Margaret E. Olson, Jianmin Lv, and Zhenyu Yao are not aware of any commercial or financial relationships that could be construed as potential conflicts of interest.

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

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