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The Role of Anti-mCRP Autoantibodies in Lupus Nephritis

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Abstract
Background: Lupus nephritis is characterized by multiple autoantibodies production. However, there are few autoantibodies associated with disease activity and prognosis. CRP exists in at least two conformationally distinct forms: native pentameric C-reactive protein (pCRP) and modified/monomeric CRP (mCRP). Autoantibodies against mCRP are prevalent in sera of patients with lupus nephritis and are reported to be pathogenic. ***Summary:*** The levels of serum anti-mCRP autoantibodies are associated with clinical disease activity, tubulointerstitial lesions, treatment response, and prognosis in patients with lupus nephritis. The key epitope of mCRP was amino acid 35–47. Furthermore, emerging evidence indicated that anti-mCRP autoantibodies could participate in the pathogenesis of lupus nephritis by forming in situ immune complexes or interfering with the biological functions of mCRP, such as binding to complement C1q and factor H. ***Key Messages:*** Here, we review the recent advances in the prevalence, clinical-pathological associations, and potential pathogenesis of anti-mCRP autoantibodies in lupus nephritis, which may provide a promising novel therapeutic strategy for lupus nephritis.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by a loss of immune tolerance, defective clearance of remnant apoptotic debris, multiple autoantibodies production, and circulating or in situ immune complex deposition, which result in various tissues and organs being damaged [1, 2]. Lupus nephritis (LN) is one of the most common and severe complications of SLE. In addition to glomerular injury, tubulointerstitial and renal vascular lesions could also be prominent in LN [3].

Plasma native pentameric C-reactive protein (pCRP) has been widely recognized as a highly conserved acute phase reactant. In contrast to other systemic inflammatory conditions, circulating pCRP levels usually remain low in active SLE [4–6]. This may be due to suppression of interleukin (IL)-6-induced CRP gene transcription and

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CRP production by overexpression of type I interferon-α (IFN-α) [7, 8] and CRP gene polymorphism [9]. It is worth noting that pCRP under specific conditions dissociates irreversibly into monomers (modified/monomeric CRP [mCRP]) and exposes new epitopes [10–14]. The physiological function of mCRP includes clearance of apoptotic cells, elimination of immune complexes, and activation/modulation of the complement system [15].

Circulating autoantibodies against mCRP have been reported in patients with SLE, especially in those with renal involvement. Levels of anti-mCRP autoantibodies were associated with clinical disease activity, tubulointerstitial lesions, treatment response, and prognosis [16–18]. Functional assays have indicated that autoantibodies against mCRP could interfere with the biological function of mCRP, which suggests a potential pathological role in LN [15].

In this review, we summarize the prevalence, clinical-pathological associations, and underlying pathogenesis of anti-mCRP autoantibodies in LN. This may pave the way for monitoring disease activity and response to therapies and provide a new target for therapeutic strategies of LN.

Immunoregulatory Functions of CRP

CRP is a highly evolutionarily conserved and ubiquitous protein in vertebrates and invertebrates [19]. The human CRP gene is located on the short arm of chromosome 1 [20]. CRP is mainly produced by hepatocytes, which can increase rapidly in response to tissue injury or infection [21]. Thus, it is regarded as a nonspecific marker for ongoing inflammation and/or infection in clinical practice. In addition, the expression of CRP has also been reported in neuronal cells [22], renal tubular epithelial cells [23], respiratory epithelial cells [24], adipocytes [25], smooth muscle cells [26], lymphocytes [27], and macrophages [28].

pCRP belongs to the pentraxin family, which consists of five identical 23 kDa nonglycosylated globular subunits arranged in a pentameric structure with discoid symmetry [29]. Two hundred and six amino acids fold into two antiparallel β-sheets with flattened jelly-roll typology and form one subunit [30]. Importantly, each protomer contains a phosphocholine-binding active site, mediating the binding of pCRP to phosphocholine exposed on apoptotic cells and bacterial cell walls [30]. The effector face is located on the opposite side of the pentamer, which could interact with the collagen-like region of the complement C1q and Fcγ receptors, and participates in the regulation of the innate immune system [31]. Under physiological conditions, the structure of pCRP has been postulated to be very stable [32]. However, accumulating studies indicate that the pentamer could dissociate into monomers under severe denaturing conditions, such as exposure to heat, high concentrations of urea, an acidic microenvironment in the absence of calcium ions [33–35]. The dissociated conformation is termed mCRP [36–39], and the neo-epitopes buried inside the pentameric structure could be exposed [40, 41]. Previous studies showed that protein denaturation was the only way to generate the monomeric forms. However, rapid dissociation of pCRP into mCRP was also found to occur on the surface of activated platelets, endothelial cells, and monocytes by binding to and interacting with membrane lipids [11, 42, 43].

CRP is a pattern recognition molecule of the innate immune system as a regulator of host defense responses [12]. In terms of removing cell debris and apoptotic cells, surface-bound pCRP activates the classical complement pathway through its binding to C1q, resulting in the formation of C3b, which acts as opsonin via binding to C3b receptors on the phagocytes [44, 45]. Furthermore, pCRP facilitates phagocytosis through binding to FcγRI and FcγRIIa receptors on phagocytes [46–49]. In addition, pCRP interacts with ficolin-2 to activate the lectin complement pathway, thus enhancing the capability of complement-mediated killing of bacteria at the early stage of the infection and participating in the clearance of apoptotic cells [50–52]. However, unlike immunoglobulin G and other triggers of the complement cascade, complement activation by pCRP is limited to the early components of the complement system, with less formation of the membrane attack complex at the terminal stage of complement activation [53]. This is owing to pCRP could also protect against overactivation of the complement system via binding to the inhibitory complement regulators of the alternative pathway, complement factor H [54, 55], and C4-binding protein (C4bp), a soluble regulator of the classical and lectin pathways [56, 57].

It is worth noting that the bioactivities of mCRP are not the same as those of pCRP. First, mCRP has a stronger binding ability with C1q compared with pCRP and has been shown to facilitate complement-dependent phagocytosis [58, 59]. Second, mCRP also acts as a regulator of the complement pathway by recruiting factor H and C4bp to injured tissues [60, 61]. Finally, mCRP, but not pCRP, can bind to factor H-related proteins 1 and 5, which enhances complement activation and facilitates opsonization [62, 63]. The

Table 1. Complement activation and regulation by pCRP and mCRP

Complement initiating molecules Complement regulatory protein	pCRP	mCRP
C1q	CP activation	CP activation
Ficolin-2	LP activation	Lack of research
C4-binding protein	CP and LP inhibition	CP inhibition
Factor H	AP inhibition	AP inhibition
Factor H-related protein 1	(–)	CP and AP activation
Factor H-related protein 5	(–)	CP and AP activation

pCRP, pentameric C-reactive protein; mCRP, modified/monomeric C-reactive protein; CP, classical pathway; LP, lectin pathway; AP, alternative pathway.

Table 2. Comparison of pCRP, mCRP, and anti-mCRP autoantibodies in patients with SLE/LN

	pCRP	mCRP	Anti-mCRP autoantibody
Local detection in renal tissue	(–)	Yes	Colocalization of mCRP and IgG
Circulating levels/prevalence	Normal	Normal	Between 4% and 78% (SLE) Between 30% and 100% (LN)
Association with disease activity	No	No	Yes
Association with treatment response	(–)	(–)	Yes
Association with prognosis	(–)	(–)	Yes

pCRP, pentameric C-reactive protein; mCRP, modified/monomeric C-reactive protein; SLE, systemic lupus erythematosus; LN, lupus nephritis.

relationship between mCRP and the complement system is extremely delicate and complex, and the stability of the immune system is maintained via a perfect balance between "activation" and "inhibition" functions (shown in Table 1). The comparison of pCRP, mCRP, and anti-mCRP autoantibodies in patients with SLE/LN is shown in Table 2.

Prevalence of Serum Anti-mCRP Autoantibodies

Serum autoantibodies against mCRP were first discovered in a patient with SLE in 1985 by Robey et al. [64]. Subsequently, several groups have confirmed the existence of autoantibodies against mCRP in SLE patients, particularly in those with LN. However, the prevalence of anti-mCRP autoantibodies in SLE patients varied between 4% and 78% [16, 65–78] and between 30% and 100% in LN [16–18, 77, 79, 80] (shown in Table 3). The differences in the reported prevalence might partly be due to the varying disease activity of enrolled patients and involvement of organs. The diverging results in these studies might also result from variations in detection methods, especially the coating antigen and blocking buffer.

Epitopes of Anti-mCRP Autoantibodies

Bell et al. [65] demonstrated the negligible capacity of pCRP to inhibit anti-CRP autoantibodies in SLE, whereas mCRP caused a dose-dependent decrease in antibody binding, indicating that the neo-epitope recognized by anti-CRP autoantibodies was only on mCRP. Subsequently, the results of inhibition assays from several studies also supported this conclusion [16, 66].

In the mid-1980s, the carboxyl-terminal octapeptide (amino acid [aa] 199–206) of mCRP, a sequence exposed only in mCRP, was described [40]. In addition, Wang et al. [41] found that aa 35–47 was the cholesterol-binding sequence, which could be unlocked by reducing the intrasubunit disulfide bridge and removing additional structural constraints on mCRP. Furthermore, Li et al. [80] synthesized a panel of 12 peptides covering the aa sequence of mCRP, and these two peptides were also found to be specifically recognized by anti-mCRP autoantibodies: aa 35–47 and aa 199–206. The autoantibodies against aa 35–47 and aa 199–206 were detected in 11/24 and 17/24 patients with LN, respectively [80]. Interestingly, only aa 35–47 could

Table 3. Prevalence of serum anti-mCRP autoantibodies in patients with SLE/LN

Year of publication	Patients, *n*	Anti-mCRP autoantibody (+)	Reference
1985	SLE (*n* = 8)	13%	[63]
1998	SLE (*n* = 50)	78%	[64]
2001	SLE (*n* = 125)	32%	[65]
2002	SLE (*n* = 27)	48%	[66]
2004	SLE (*n* = 10), LN (*n* = 4)	70%, 100%	[15]
2006	SLE (*n* = 190)	23%	[67]
2006	SLE (*n* = 137)	51%	[68]
2007	SLE[1] (*n* = 100), SLE[2] (*n* = 50)	10%, 4%	[69]
2007	SLE (*n* = 125)	40%	[70]
2008	Active LN (*n* = 96)	59%	[16]
2009	SLE (*n* = 92)	37%	[71]
2009	LN (*n* = 38)	45%	[78]
2010	SLE[a] (*n* = 39), SLE[b] (*n* = 42)	26%, 13%	[72]
2011	SLE (*n* = 39)	62%	[73]
2013	SLE (*n* = 100)	26%	[74]
2014	SLE (*n* = 99)	18%	[75]
2015	Active LN (*n* = 46)	33%	[17]
2017	SLE (*n* = 31), LN (*n* = 56)	45%, 76%	[76]
2017	LN (*n* = 80)	30%	[79]
2018	SLE (*n* = 34)	53%	[77]

SLE, systemic lupus erythematosus; LN, lupus nephritis; mCRP, modified/monomeric C-reactive protein. [1]SLE: patients with quiescent disease (median European Consensus Lupus Activity Measurement [ECLAM] score 2). [2]SLE: patients with active disease (median Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] score 16). [a]SLE: patients with high disease activity (British Isles Lupus Assessment Group [BILAG] A or B scores). [b]SLE: patients with low disease activity (no BILAG A or B scores).

efficiently inhibit antibody binding to immobilized mCRP. Therefore, aa 35–47 was considered the major epitope of mCRP [80].

Clinical Significance of Serum Anti-mCRP Autoantibodies

Serum Anti-mCRP Autoantibodies Are Associated with LN

In 2004, Sjöwall et al. [16] reported that all 4 patients with active LN were serum anti-mCRP autoantibodies positive. Their further studies demonstrated that the prevalence of anti-mCRP autoantibodies was higher in proliferative nephritis compared with that in membranous nephritis [79]. Figueredo et al. [69] found that the prevalence of anti-mCRP autoantibodies was higher in patients with kidney involvement than those without (27% vs. 13%). Similarly, our previous studies have also shown that the prevalence of mCRP autoantibodies in active LN was significantly higher than that in SLE patients without kidney involvement [17]. In addition, our findings were later confirmed by Jakuszko et al. [77], who demonstrated that the positive anti-mCRP autoantibodies were observed in 35 (47.3%) patients with LN, compared to 7 (24.1%) nonrenal SLE patients. The above studies showed that the presence of anti-mCRP autoantibodies is closely associated with LN.

Levels of Serum anti-mCRP Autoantibodies Are Associated with Disease Activity of SLE/LN

Sjöwall and Jung et al. [16, 76] reported that levels of serum anti-mCRP autoantibodies were positively associated with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores and levels of anti-dsDNA antibodies and negatively associated with the levels of C3 and C4 in patients with SLE. In addition, SLE patients with anti-mCRP autoantibodies showed increased prevalence of anti-dsDNA antibodies, antiphospholipid antibodies, higher levels of tumor necrosis factor-α (TNF-α), lower CH50 activity, and decreased levels of complements compared to those without [69, 75, 77].

Further studies focused on the subgroup of patients with LN. Our study found that patients with anti-mCRP autoantibodies were more likely to have higher SLEDAI scores and more acute kidney injury [17]. Interestingly, a correlation between the levels of anti-mCRP autoantibodies and scores of renal tubulointerstitial lesions was noted in patients with LN [17] and further verified in

patients with tubulointerstitial nephritis and uveitis (TINU) syndrome [81] and acute tubulointerstitial nephritis [82]. In a later study that enrolled 38 patients with LN, levels of anti-mCRP autoantibodies were reported to be associated with the renal biopsy activity index [79]. Our study has revealed that patients with anti-$mCRP_{35-47}$ autoantibodies had more severe kidney injury than those without, as evidenced by the higher activity index and chronicity index scores [80].

Tan et al. [17] reported that LN patients with positive anti-mCRP autoantibodies in the active phase turned negative in remission. In addition, Jakuszko et al. [77] found that the prevalence of anti-mCRP autoantibodies was decreased after standard treatment in patients with LN. There was also a significant decrease in the concentrations of IL-6, TNF-α, proteinuria, SLEDAI scores and an increase in CH50 activity. The above studies indicated that the levels of anti-mCRP autoantibodies were associated with clinical disease activity and kidney involvement, especially tubulointerstitial lesions in LN.

Levels of Serum Anti-mCRP Autoantibodies Are Associated with Treatment Response and Prognosis of SLE/LN

Previous studies have identified that the presence of serum anti-mCRP autoantibodies in LN is superior to that of anti-dsDNA antibodies in predicting poor response to therapies [79]. Furthermore, a large longitudinal study from Europe reported delayed therapeutic response in patients with LN with positive anti-mCRP autoantibodies. In addition, patients with positive anti-mCRP autoantibodies were more likely to relapse during follow-up (a median of 5.9 years), even in partial/complete response, which suggests that anti-mCRP autoantibodies might be an important predictor of renal flares. More importantly, the presence of anti-mCRP autoantibodies at baseline seems to be a predictor for poor prognosis, including nonresponse, renal flare, or end-stage renal disease after 2 years of standard treatment [18]. More recently, our study showed that the presence of anti-$mCRP_{35-47}$ autoantibodies was an independent risk factor for renal outcomes with an average follow-up of 48 months for patients with LN [80].

Role of Serum Anti-mCRP Autoantibodies in the Pathogenesis of SLE/LN

As mentioned above, a high prevalence of serum anti-mCRP autoantibodies has been reported in patients with SLE, especially in those with LN. In addition, levels of anti-mCRP autoantibodies could be used as biomarkers to monitor clinical disease activity and evaluate treatment response and prognosis. Therefore, the pathogenic role of anti-mCRP autoantibodies is controversial.

Previous studies showed that autoantibodies against mCRP in LN could inhibit the complement activation of the classical pathway by interfering with the binding between mCRP and C1q, and the deposition of C3b on late apoptotic cells was significantly decreased. This may lead to the reduced phagocytosis of apoptotic materials and more self-antigens might be exposed to the immune system, resulting in the continuous production of multiple autoantibodies and the formation of a vicious cycle, ultimately resulting in tissue damage and organ dysfunction [15]. Additionally, Li et al. [80] have found that mCRP might be able to inhibit the excessive activation of complement alternative pathway and the generation of membrane attack complex via the binding of mCRP aa 35–47 and complement factor H. In contrast, the autoantibodies recognizing this epitope could interfere with the binding affinity between complement factor H and mCRP, which might interfere with the regulatory function of complement factor H, leading to the overactivation of complement pathway and kidney injury. Taken together, these observations suggest that mCRP could trigger or regulate complement activation, and anti-CRP autoantibodies might contribute to the pathogenesis of LN by interrupting the biological functions of mCRP in the clearance of apoptotic cells and regulation of complement activation.

Previous studies have shown that the expression of mCRP was mainly detected in the renal tubules and interstitium of patients with TINU syndrome [81, 83]. Similarly, Schwedler et al. [84] found that the levels of tubular mCRP staining were associated with declining renal function and increasing severity of histological lesions in patients with advanced diabetic nephropathy. These findings support the increased expression of mCRP in renal tubulointerstitial injury. However, the local production of mCRP is still unclear. Some researchers speculate that plasma pCRP is deposited in renal tissue or is directly synthesized in situ by renal tubular epithelial cells or infiltrated lymphocytes. Then, pCRP under the acidic microenvironment of inflammatory tissue or other certain circumstances may dissociate into mCRP, which could constitute a target for anti-mCRP autoantibodies [61]. In addition, the direct in situ synthesis and secretion of mCRP cannot be excluded.

Notably, CRP was colocalized with IgG in electron-dense deposits in the glomerular basement membrane/subendothelial space in all 5 patients with LN that have

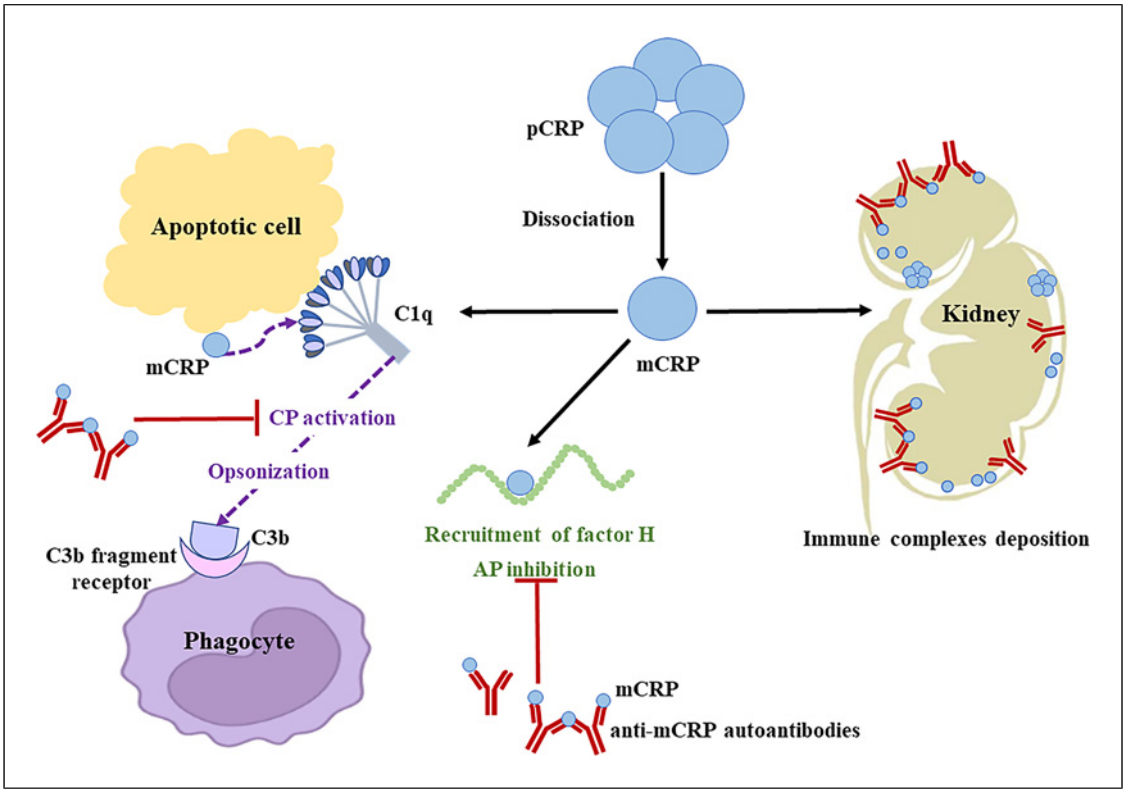

Fig. 1. Role of anti-mCRP autoantibodies in the pathogenesis of LN. (1) pCRP under inflammatory conditions may dissociate into mCRP; (2) anti-mCRP autoantibodies could inhibit the complement activation of the classical pathway via interfering with the binding between mCRP and C1q, resulting in reducing complement-dependent phagocytosis; (3) anti-mCRP autoantibodies could interfere with the binding affinity between complement factor H and mCRP, leading to the overactivation of alternative complement pathway; (4) anti-mCRP autoantibodies and mCRP might form in situ renal immune complexes, which may eventually initiate or amplify inflammation. pCRP, pentameric C reactive protein; mCRP, modified/monomeric C reactive protein; CP, classical pathway; AP, alternative pathway.

been observed by high-resolution immunogold electron microscopy [85]. In subsequent investigations, double staining by immunofluorescence revealed that mCRP was deposited in tubules, and the colocalization of mCRP and IgG could be detected in patients with TINU syndrome [81]. Since mCRP was found to colocalize with IgG, it is probable that this actually represents immune complexes composed of mCRP-anti-CRP antibodies. Similar to anti-dsDNA antibodies and anti-C1q antibodies [86, 87], it is reasonable that anti-mCRP autoantibodies and mCRP might form in situ renal immune complexes, which may subsequently lead to local complement activation and recruitment of leukocytes, eventually initiating or amplifying inflammation in the target organs. More interestingly, the formation of ectopic germinal centers in the tubulointerstitium may contribute to the production of pathogenic autoantibodies. Germinal center-like structures, including follicular dendritic cells, were observed in 8% of renal biopsies [88]. More commonly, well-formed aggregations of B cells and T cells can be seen in up to 50% of renal biopsies [88]. Lymphoid-like histological structures indicate that locally appearing antigens are derived in situ from B-cell and T-cell selection and then produce autoantibodies with high affinity for various antigens. Kinloch et al. [89] found that vimentin could activate local antigen-presenting cells, elicit in situ adaptive immune response, and lead to immune complex deposition and more inflammation in lupus tubulointerstitial nephritis.

Conclusions

A high prevalence of serum anti-mCRP autoantibodies in patients with LN has been widely accepted, and the serum levels of anti-CRP autoantibodies were associated with clinical disease activity, often indicating a high risk of flares. In addition, the presence of autoantibodies

against mCRP is associated with more severe renal damage and predicts a worse outcome. Thus, serum anti-mCRP autoantibodies could be a biomarker to reveal disease activity and predict clinical prognosis in patients with LN. Currently, it has been postulated that anti-mCRP autoantibodies might participate in the pathogenesis of LN by interfering with the biological roles of mCRP or forming in situ immune complexes (shown in Fig. 1). However, limited evidence is available at present. In the future, the exact role of anti-mCRP autoantibodies in the pathogenesis of LN, particularly in the tubulointerstitial lesions, needs to be further verified using animal models. Thus, explorations of the pathogenesis of LN will identify targeted therapeutic interventions. For instance, designing a modified peptide that can inhibit the formation of mCRP-anti-mCRP autoantibody immune complexes might provide a therapeutic option for LN.

Conflict of Interest Statement

The authors have declared no conflicts of interest.

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Author Contributions

Mo Yuan wrote the first draft of the manuscript. Yin Tan and Ming-hui Zhao revised the manuscript. All the authors contributed to the article and approved the final submitted version.

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