

Antibodies against Pentraxins and Lupus Nephritis Activity

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Abstract

Impaired apoptosis and dysfunction of the immune cells are considered to be the most important pathogenic mechanisms of systemic lupus erythematosus. Pentraxins, which are natural opsonins, are directly involved in the removal of cellular material by binding to different antigens and initiating and enhancing phagocytosis of damaged cells. Therefore the deficiency of pentraxins is a crucial risk factor for the development and progression of systemic lupus erythematosus.

Despite the presence of elevated levels of interleukin-6, which under physiological conditions increases the expression of acute phase protein genes, in systemic lupus a deficiency of C reactive protein and other pentraxins is observed. Several mechanisms responsible for pentraxin deficiency have been postulated, including the impairment of pentraxin synthesis due to mutations in genes, gene inhibition by interferon- α , and removal of pentraxins by autoantibodies.

In this review, we summarize the significance of antibodies directed against pentraxins in assessing the activity and severity of systemic lupus erythematosus and lupus nephritis, as well as the usefulness of these antibodies as an additional marker of the response to treatment. The role of antibodies directed against monomeric C reactive protein in the pathogenesis of lupus nephritis is also discussed, as these antibodies are considered as a factor causing damage to the glomerular cells.

Keywords: Pentraxins; Antibodies; Lupus nephritis

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with complicated pathogenesis, significant clinical manifestations and variable responses to treatment. The impaired apoptosis and dysfunction of the immune cells, including T and B lymphocytes and dendritic cells, lead to the accumulation of undegraded, strongly immunogenic cellular material and a loss of immunological tolerance to antigens [1]. These complex immune disorders may be induced by genetic, environmental, as well as hormonal factors and are considered as one of the most important pathogenic mechanisms of SLE development and progression [2].

In physiological conditions the damaged cells are surrounded by opsonins (including complement components, collectins and pentraxins), which allow the recognition of antigens by Fc γ receptors on the surface of phagocytes (Fc γ RI, Fc γ RII and Fc γ RIII) and initiation of phagocytosis. The apoptotic cells are then combined with lysosomes containing deoxyribonuclease (DNase), leading to the degradation of the chromosomal deoxyribonucleic acid (DNA) to nucleosomes and then to nucleotides [3].

In SLE patients the removal of apoptotic material by macrophages is impaired, so that it becomes accessible to antigen-presenting cells. The main sources of antigens in SLE are anionic phospholipids, nucleosomes and ribonucleoproteins, which are transferred from intracellular compartments and presented on the surface of dying cells. Due to impaired apoptosis, autoantigens are not removed; they

stimulate secretion of interferon- α (IFN- α) and initiate the immune response [4]. As a result of overstimulation by antigens, in the presence of proinflammatory cytokines (such as IFN- α), the formation of autoreactive T and B cells is started. Activated B lymphocytes produce autoantibodies that bind to the antigens and complement components to form immune complexes, which may be deposited in tissues, stimulate the secretion of proinflammatory cytokines and proteolytic enzymes, and cause inflammation and organ damage [2,5,6].

Opsonin Deficiency and SLE Pathogenesis

Complement components, collectins and pentraxins are natural opsonins, which have the greatest significance in the process of apoptosis. They are directly involved in the removal of cellular material by binding to different antigens and initiating and enhancing phagocytosis of damaged cells [7]. A deficiency of serum opsonins is now considered as a crucial risk factor for SLE development and progression [8-10].

Complement components

Complement components, which increase the activity of phagocytes and thereby enable the uptake and elimination of damaged cells, are necessary during all stages of apoptosis. The cascade of enzymatic reactions leading to the formation of C3 and C5 convertases and the activation of the cell killing membrane attack complex (MAC) is a result of complement activation by the classical, alternative or lectin pathway. Binding C1q component to antibodies or other proteins (for example pentraxins) is the first element of the classical complement

activation pathway. By the direct activation of C3 component the formation of crucial enzymes by an alternative pathway is started. The lectin pathway is initiated with the participation of the collectins, which are opsonins binding to microbial polysaccharide coatings [3].

It has been shown that in the case of components C1q, C2 and C4 deficiency the opsonization of antigens is less efficient, and the accumulated cellular material is not removed, which stimulates secretion of proinflammatory cytokines and activates dendritic cells, monocytes, macrophages and effector lymphocytes [6]. Additionally, IFN- α stimulates the activation of autoreactive T cells, which favors the initiation of an inflammatory reaction within the tissue and the development of chronic autoimmunity [11-13].

Collectins

Collectins by binding to oligosaccharide structures of cell membranes, participate in pathogen recognition, activating the lectin pathway of the complement system and initiating phagocytosis. Mannan binding lectin (MBL), one of the acute phase proteins synthesized in the liver, is the best known collectin. MBL is structurally similar to complement component C1q. Serine proteases associated with MBL (MASP 1, 2 and 3) are structurally similar to C1q, C1r and C1s components and responsible for the activation of the complement system [14].

The presence of polymorphisms and single mutations in genes encoding MBL, found in patients with SLE, may be the cause of low concentrations of MBL in serum [12,15].

Pentraxins

Pentraxins, which are acute phase proteins, have a special role in apoptosis. By recognizing pathogens and damaged own cells, enhancing phagocytosis and stimulating classical complement pathway activation, pentraxins are involved in hiding antigens from the immune system. Pentraxins are glycoproteins composed of five or ten polypeptide subunits. C-reactive protein (CRP), which has a molecular weight 21 kDa of each subunit [16], and serum amyloid P (SAP), with a molecular weight 25.5 kDa of each subunit [17], are classified as short pentraxins. Long pentraxin 3 (PTX3) differs from short pentraxins by the higher molecular weight of a subunit (40.1 kDa) and the length of the N-terminal region. Pentraxin subunits are connected by non-covalent bonds and arranged in a pentamer (CRP) or decamer (SAP and PTX3) with radial symmetry [18].

Pentraxin secretion increases during infection, inflammation and tissue injury and is stimulated by cytokines, including interleukin 6 (IL-6), interleukin 1 β (IL-1 β) and tumor necrosis factor alpha (TNF- α) [19]. Secretion of CRP and SAP by hepatocytes is stimulated by IL 6, which is one of the major inducers of the C reactive protein gene during the acute phase response [20]. Following activation by IL 6 in the liver the transcriptional factors regulating gene expression of acute phase proteins—liver activating protein (LAP) and the signal transducer and activator of transcription 3 (STAT 3)—enhance the transcription of messenger RNA (mRNA) and the synthesis of CRP [21].

C reactive protein was discovered over 80 years ago in sera of patients with pneumonia caused by *Streptococcus pneumoniae*. The name of CRP was influenced by the reaction with the C polysaccharide present in the coat of bacteria and providing resistance to phagocytosis [20]. CRP subunits have a spherical shape and the ability to connect to

different ligands involving calcium ions. Within each subunit the specific binding sites for complement component C1q and macrophage Fc γ receptors are present [22]. Due to the structure of CRP, and the size of C1q and Fc γ R, only one ligand can be bound to each pentamer of CRP [23]. SAP and PTX3 also bind to Fc γ receptors, which stimulate opsonization of pathogens and damaged own cells and allow the proper course of phagocytosis [18,24]. There is evidence that C reactive protein is also produced by renal tubular epithelium, neurons, lymphocytes, smooth muscle cells and alveolar macrophages, but the mechanisms for stimulating the synthesis of CRP in these organs are not known [25]. Pentraxin 3 is produced in the tissues by mononuclear cells in response to IL 1 β and TNF α and upon stimulation of lipopolysaccharide [26].

In SLE, autoantibodies are formed against nuclear and nucleolar antigens. Binding of these antigens by pentraxins results in faster antigen removal and prevents autoimmunity. C reactive protein binds to the cell membranes of damaged cells by interaction with complement complex, small nuclear ribonucleoprotein (snRNP) and chromatin by the interactions with histones. The strongest interactions were observed between CRP and histones H1 and H2A, weaker with H2B, H3 and H4. There was no interaction between CRP and native DNA [22]. It has been shown that CRP connects with an amino acid domain of H2A and the carboxyl terminal domain of H1. SAP is bound to chromatin and nucleolar antigens and PTX3 to the histones and cell membranes of apoptotic cells [19,27].

It was also found that surrounding the apoptotic cells by pentraxins accelerates their opsonization and phagocytosis by interaction with Fc γ receptors of phagocytes and increases the release of inflammatory and chemotactic cytokines by macrophages [28]. Short pentraxins connect with all types of Fc γ receptors, but CRP shows the greatest affinity for Fc γ RI and Fc γ RII of monocytes and macrophages and SAP for Fc γ RIII of macrophages, neutrophils and NK cells [29]. Pentraxin 3 binds only to Fc γ RIII, which suggests its pivotal role in activating neutrophils and NK cells [16].

Another mechanism which accelerates the removal of apoptotic material by pentraxins is their participation in the activation of the classical complement pathway. This is enabled by combining pentraxins with specific sequences of C1q complement component [19]. CRP and SAP, after the binding of ligands such as snRNP and histones, undergo structural changes which involve exposure of specific binding sites for C1q [30]. PTX3 binds to C1q in unchanged form, but this interaction activates the complement cascade less strongly [31].

The activation of the complement system with the involvement of C reactive protein is different from the activation by antibodies. CRP is involved in the activation of the classical complement pathway, especially during the early phase of the process. However, CRP has an inhibitory effect on the later stages, which causes a decrease in the production of MAC. The opposing effect of CRP during different stages of activation of complement is important, because CRP stimulates the opsonization of apoptotic cells, but on the other hand protects them from excessive damage, lysis and release of proinflammatory cytokines [27,32].

Pentraxin deficiency in SLE

In SLE, despite the presence of elevated levels of IL 6, which under physiological conditions increases the expression of the C reactive protein gene, deficiency of CRP and other pentraxins is observed. It

has been proved that, similar to deficiency of complement components, pentraxin deficiency impairs the removal of cellular material, leading to an increased immune response, secretion of autoantibodies directed against different antigens, deposition of immune complexes in organs, and consequently disease development and progression [27].

Low concentrations of CRP, in contrast to the concentrations of other acute phase proteins and with high levels of IL 6, are characteristic mainly for exacerbations of SLE. In contrast to other rheumatic diseases, such as rheumatoid arthritis, in SLE patients no association between serum IL 6 and C reactive protein has been found [33-35]. However, in a recently published study in patients with low IFN α levels, a relationship between serum CRP levels and IL 6, as well as disease activity, expressed by the SLE Disease Activity Index (SLEDAI), was described [36].

Low CRP concentrations and a weak CRP response during infections are also typical for SLE patients. However, during severe bacterial infections, an increase in concentrations of acute phase proteins, including CRP, may be present [37]. Moreover, high levels of C-reactive protein can be constantly observed in patients with chronic synovitis and the chronic deforming arthritis occurring in 10-35% of patients with SLE (Jaccoud's arthritis) [21]. The reason for this phenomenon is not clear, but it is believed that chronic synovitis with the presence of many inflammatory cells causes the production of high concentrations of cytokines (IL 1, IL 6), which stimulate the synthesis of acute phase proteins, including CRP [38].

Several possible mechanisms responsible for pentraxin deficiency in SLE have been considered, including the impairment of CRP synthesis due to mutations in genes [39,40], gene inhibition by IFN α [41], and CRP removal by autoantibodies [34].

Firstly the pentraxin deficiency may result from a defect in their synthesis. A genetic defect in the synthesis of CRP and SAP is associated with the presence of the mutations in genes for these proteins, located on the short arm of chromosome 1 (1q23.2). Various genetic polymorphisms, which cause the presence of low concentrations of serum CRP and SAP, with simultaneous formation of antinuclear antibodies, leading to the development and progression of SLE, have been described in the literature [39,40].

Impaired synthesis of CRP in patients with SLE can also result from inhibition of the CRP gene by IFN- α , whose role in the pathogenesis of SLE was confirmed in previous studies [42]. Besides the influence of IFN- α on the impairment of apoptosis by the inhibition of pentraxin synthesis, IFN- α plays an important role in the development and progression of SLE by increasing the expression of cytokines and chemokines and by stimulating the differentiation of monocytes into active dendritic cells. IFN- α also stimulates the maturation of B lymphocytes and the formation of plasma cells, producing autoantibodies [43,44].

Increased expression of transcriptional factors, regulated by IFN- α and inhibiting the synthesis of CRP, plays an important role in the pathogenesis of SLE [41]. Under normal conditions, as a result of stimulation by IL 6, liver transcriptional factors LAP and STAT 3, regulating the expression of acute phase protein genes, increase the transcription of mRNA and synthesis of CRP. In an experimental model it was confirmed that, in response to IFN- α , the inhibition of these factors and the activation of proteins that act oppositely—liver inhibitory protein (LIP) and the signal transducer and activator of

transcription 1 (STAT 1)—result in a decrease of the production of CRP, despite the high level of IL-6 [21,27,41].

A third theory of low pentraxin concentrations in SLE concerns the disposal of pentraxins by binding with the anti pentraxin antibodies detected in the serum. However, in most studies, there was no significant correlation between low levels of C-reactive protein and concentrations of antibodies directed against CRP. Therefore the presence of these antibodies cannot explain the low concentrations of C-reactive protein in the serum and weak CRP increase in response to infection [21]. However, the role of antibodies against CRP in the pathogenesis of the disease has been recently postulated. The presence of anti-CRP antibodies binding to the cell surface and forming immune complexes, accumulated within the different organs, was confirmed [45].

Antibodies against CRP and Lupus Nephritis

Antibodies against C-reactive protein, detected in the serum of patients with SLE, are not directed against the native, pentameric CRP, but against modified monomeric CRP, which has different physicochemical, antigenic and electrophoretic properties [46]. Irreversible conversion from pCRP to mCRP takes place in certain conditions such as lowered pH, high urea concentration or low calcium levels, and depends on the loss of the secondary structure and formation of an alpha-helix structure [47].

The presence of anti-mCRP antibodies (anti-mCRP Abs) was found in the serum of 23-78% of patients with SLE, 30% of patients with subacute cutaneous lupus erythematosus (SCLE) and in 7.5% of patients with discoid lupus erythematosus (DLE) [34,46,48,49]. The production of these antibodies was most common for patients with active renal involvement [50].

In most of the studies the presence of antibodies against monomeric CRP in patients with active lupus nephritis (LN) was confirmed [45,50-52]. Significant correlations between the concentrations of anti-mCRP Abs and clinical and immunological indicators of activity of LN were found. This points to the possibility of their use as an indicator for determining the activity and severity of the disease, as well as an additional marker providing lupus nephritis flares and the response to treatment [50].

The studies performed in our center confirmed the usefulness of anti-mCRP Abs in the evaluation of clinical activity of lupus nephritis. Both higher incidence and higher levels of these antibodies in patients with lupus nephritis compared to patients without renal involvement were described. Relationships between anti-mCRP Abs and classical, as well as novel but well-documented indicators of SLE activity (serum levels of cytokines IL-6 and TNF- α), were also found. A statistically significant decrease in the concentration of anti mCRP Abs in the course of treatment was observed, which confirmed that measuring the levels of these antibodies allows one to monitor the disease activity and can be used in evaluating the effectiveness of treatment [53].

Anti mCRP Abs are considered as a factor causing damage to the glomerular cells, mainly by increasing the amount of circulating pathogenic immune complexes [10]. The presence of monomeric CRP within the glomerular structure was confirmed in recent studies [54] and the presence of immune complexes was found in the biopsy material within the mesangial cells and capillary wall [55].

Moreover, in one report it was suggested that higher concentrations of antibodies against monomeric CRP in patients with lupus nephritis

class III and IV compared to patients with membranous nephropathy may indicate the role of anti-mCRP Abs as a biomarker characteristic for proliferative LN [50]. In our study the levels of anti-mCRP Abs were significantly higher in class V LN compared to the other LN types [53]. Another study did not confirm the relationship between the type of lupus nephritis and the anti-mCRP antibody levels [52]. Therefore further investigations on the relationship between these antibodies and the type of histopathological changes are needed.

Under normal conditions, the complexes consisting of mCRP and antibodies should be eliminated by the liver by the influence of complement components C1q, C3 and C4, after binding to the Fc γ receptors of macrophages or receptors for complement of red blood cells (CRI) [56]. The reduced complement hemolytic activity, as well as Fc γ receptor gene mutations, causing the presence of low affinity receptors for immunoglobulin G in SLE patients, inhibits the removal of circulating immune complexes containing anti-mCRP antibodies. This promotes the deposition of immune complexes within the glomeruli, leading to the activation of cytotoxic lymphocytes and the inflammatory process [39].

The complexes containing mCRP and antibodies initiate or exacerbate inflammation synergistically with other antibodies (including anti-C1q, anti-dsDNA and anti- α actinin) [57].

There is empirical evidence that anti-mCRP Abs also directly damage the structure of the glomeruli by connecting with endogenous glomerular antigens such as monomeric CRP, whose presence within the glomerular structure was confirmed in recent studies [54]. It was also found that the mCRP may be exposed on the cell surface and by binding to immunoglobulins may form immune complexes *in situ* [45,58].

Antibodies against CRP In Other Diseases

Despite the high prevalence of anti-mCRP Abs in LN, these antibodies are not specific for SLE. The presence of anti-mCRP Abs has also been demonstrated in approximately 7-22% of patients with other autoimmune diseases, including systemic sclerosis, rheumatoid arthritis, Sjögren's syndrome, primary biliary cirrhosis and autoimmune hepatitis. However, the incidence of these antibodies in other autoimmune diseases was significantly lower than in SLE patients [46,48,49,59].

Positive anti-mCRP Abs were observed in all patients with the tubulointerstitial nephritis and uveitis syndrome (TINU), which is characterized by the presence of active nephritis with concomitant uveitis. Monomeric CRP, which is expressed in both tubular epithelial and uveal cells, is considered as a target antigen in this disease [60]. Tubular deposition of mCRP was confirmed by immunohistochemical staining using a mouse monoclonal antibody against human mCRP in a TINU patient treated in our center [unpublished data].

Antibodies against Other Pentraxins

Low concentrations or inactivity of other pentraxins (SAP and PTX3) are characteristic for SLE. Some reports suggest that this may result from the presence of autoantibodies [61].

The presence of antibodies against serum amyloid P (anti-SAP Abs) was found in 20-44% of patients with SLE. A relationship between the concentrations of these antibodies and clinical and immunological activity of SLE, determined by the titers of SLEDAI index, antinuclear and anti-dsDNA antibodies, was detected. Similarly to anti mCRP

Abs, the decrease in the concentrations of anti SAP Abs preceded the remission and the increase appeared before clinical exacerbation of SLE, which suggests the possibility of using anti-SAP as an additional prognostic marker. In contrast to anti-mCRP Abs there was no association between the presence of anti-SAP Abs and the clinical manifestations of SLE [34,62].

The presence of antibodies against long pentraxin 3 (anti-PTX3 Abs) in 50% of patients with SLE was also described. It was found that the concentrations of these antibodies correlated with classical indicators of disease activity—positively with antinuclear and anti-dsDNA Abs and negatively with the concentrations of complement components and the number of leukocytes [63]. In another study the presence of anti-PTX3 Abs and against peptides isolated from PTX3 with strong immunogenic properties was determined, showing the presence of these antibodies in 46% and 37%-61% of patients with SLE, respectively. In this study, the relationship between antibody titers and disease activity was not confirmed. The highest concentrations of anti-PTX3 Abs were found in patients without lupus nephritis, which might suggest the protective role of these antibodies. The protective role of anti-PTX3 Abs could be the result of the competitive effect on, among others, anti-C1q, whose association with lupus nephritis development and progression was documented [64]. However, the problem of antibodies against other pentraxins still remains unresolved [63].

Conclusion

In summary, the association of opsonin deficiency and development or progression of systemic lupus erythematosus indicates the crucial role of complement components, collectins and pentraxins in protection from autoimmunity. Although antibodies against pentraxins may not be a cause of their low concentrations, the presence of these antibodies and the role of antibodies against monomeric CRP in the pathogenesis of lupus nephritis was confirmed in recently published studies. Moreover, the usefulness of anti-mCRP antibodies in assessing the disease activity and severity, especially the relationship with active lupus nephritis, may be used in clinical practice.

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