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Review

Antibodies targeting circulating protective molecules in lupus nephritis: Interest as serological biomarkers

Chantal Dumestre-Pérard[a,b,*], Giovanna Clavarino[a,b], Sophie Colliard[a], Jean-Yves Cesbron[a,b], Nicole M. Thielens[c]

[a] Laboratoire d'Immunologie, Pôle de Biologie, CHU Grenoble Alpes, CS 10217, 38043 Grenoble Cedex 9, France
[b] BNI TIMC-IMAG, UMR5525, CNRS-Université Grenoble Alpes, BP170, 38042 Grenoble Cedex 9, France
[c] Univ. Grenoble Alpes, CNRS, CEA, IBS, F-38000 Grenoble, France

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ABSTRACT

Lupus nephritis (LN) is one of the most frequent and severe manifestations of systemic lupus erythematosus (SLE), considered as the major predictor of poor prognosis. An early diagnosis of LN is a real challenge in the management of SLE and has an important implication in guiding treatments. In clinical practice, conventional parameters still lack sensitivity and specificity for detecting ongoing disease activity in lupus kidneys and early relapse of nephritis. LN is characterized by glomerular kidney injury, essentially due to deposition of immune complexes involving autoantibodies against cellular components and circulating proteins. One of the possible mechanisms of induction of autoantibodies in SLE is a defect in apoptotic cells clearance and subsequent release of intracellular autoantigens. Autoantibodies against soluble protective molecules involved in the uptake of dying cells, including complement proteins and pentraxins, have been described. In this review, we present the main autoantibodies found in LN, with a focus on the antibodies against these protective molecules. We also discuss their pathogenic role and conclude with their potential interest as serological biomarkers in LN.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of a large number of autoantibodies (about 180, reviewed in [1]) at the origin of systemic inflammation and by multi-organ manifestations including dermatological, musculoskeletal, renal, cardiac, vascular and pulmonary symptoms [2]. The disease course, characterized by an alternation of flares and remissions, makes the patient care difficult given the unpredictability and diversity of manifestations. Lupus nephritis (LN) is one of the most frequent and severe complications of SLE, progressing to end-stage renal disease in up to 30% cases and exposing the patient to a significantly increased mortality risk [3, 4]. An early diagnosis of LN is a real challenge in the management of SLE and has an important implication in guiding treatments [5]. Renal damages mainly affect the kidney glomerulus with various localizations including endothelial cells, epithelial cells, mesangial cells and podocytes, but tubulointerstitial and vascular lesions can also be observed. Different classes of glomerular nephritis are defined according to the histologic characteristics of the lesions and the immune deposits, observed on renal biopsies by optical microscopy and immunofluorescence, respectively [6, 7]. Conventional laboratory markers include proteinuria, urinary protein-to-creatinine ratio and creatinine clearance for evaluation of renal activity, and serum complement and anti-dsDNA antibodies as immunological biomarkers related to the level of inflammation [8]. However these parameters lack sensitivity and specificity for detecting ongoing or relapsing disease activity in lupus kidneys, emphasizing the need for novel biomarkers for LN diagnosis and prediction of LN outcomes.

Possible mechanisms for the genesis of renal lesions include (i) intrarenal deposit of circulating immune complexes (ICs) and/or (ii) *in situ* formation of ICs from autoantibodies recognizing renal parenchyma antigens or circulating antigens (DNA and nucleosomes) bound to constituents of the glomerular basement membrane and/or (iii) vascular microthrombosis possibly linked to anti-phospholipid syndrome. Intrarenal inflammation is amplified through complement activation by the immunoglobulin components of ICs and the recruitment of inflammatory cells. The major etiology proposed for the presence of nuclear antigens in the circulation is a defect in apoptotic cells clearance, leading to secondary cell necrosis and subsequent release of intracellular autoantigens [9]. Apart from antibodies against nuclear antigens and kidney cells components, autoantibodies against serum

* Corresponding author at: Laboratoire d'Immunologie, Pôle de Biologie, CHU Grenoble Alpes, CS 10217, 38043 Grenoble Cedex 9, France.
E-mail address: cdumestre-perard@chu-grenoble.fr (C. Dumestre-Pérard).

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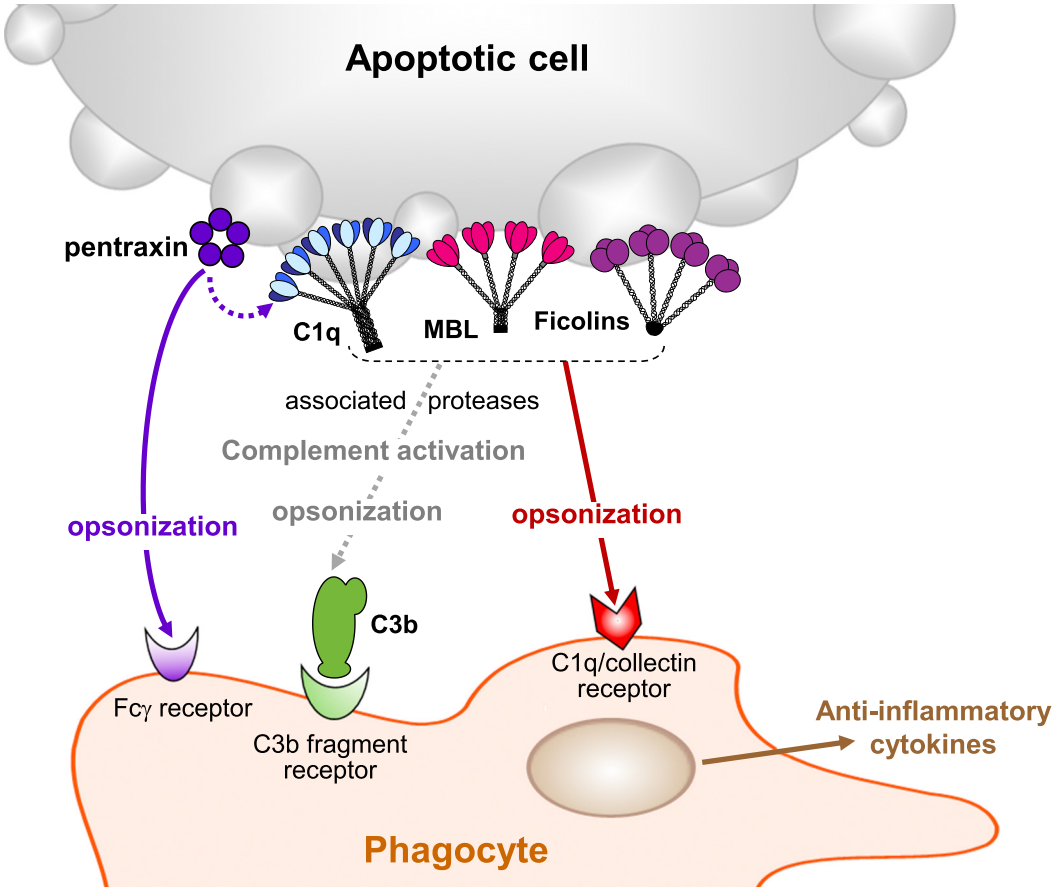

Fig. 1. Role of circulating protective molecules in the clearance of apoptotic cells.
Pentraxins and the complement recognition proteins C1q (classical pathway) and MBL or ficolins (lectin pathway) bind to molecular motifs at the surface of apoptotic cells. They act as bridging molecules to facilitate phagocytosis of the opsonized cells through interaction with phagocyte complement receptors, which triggers an anti-inflammatory response. Limited complement activation occurs on apoptotic cells and deposited C3b also contributes to the immunologically safe clearance of apoptotic cells.

protective molecules involved in the uptake of dying cells have been described, including C1q, MBL, pentraxins [10], and more recently C3b and ficolins-2 and -3 [11–14]. All these proteins bind to apoptotic cell-associated molecular patterns and facilitate phagocytosis of the opsonized cells through interaction with phagocyte receptors while triggering an anti-inflammatory response. Limited complement activation occurs on apoptotic cells and deposited C3b also contributes to the immunologically silent clearance of apoptotic cells (Fig. 1).

In this review we describe the main autoantibodies found in LN with a focus on the antibodies against circulating protective molecules, discuss their pathogenic role and conclude with their potential interest as part of serum multi-panel biomarkers in LN.

2. Autoantibodies against cell components in lupus nephritis

2.1. Anti-nuclear antibodies

2.1.1. Anti-dsDNA antibodies

First identified in the blood of SLE patients 60 years ago, anti-double-stranded DNA (dsDNA) autoantibodies have been suggested to play a pathogenic role in LN following their detection in glomeruli of LN patients [15]. Anti-dsDNA antibodies have been intensively investigated since, both in serum and in kidney deposits and numerous controversial results have been reported. They have a high prevalence in SLE and LN patients (Table 1) and their serum levels are part of the conventional markers of active renal disease (together with anti-C1q antibodies and complement levels). However, they have widely variable sensitivity and specificity, depending on the measurement method (radioimmunoassay, indirect immunofluorescence test and enzyme-linked immunosorbent assays) and the DNA antigen (of bacterial, protozoan and mammalian sources) used. In fact, no clear correlation has been observed reproducibly between serum anti-DNA antibodies and the type or severity of renal disease, casting doubts about their utility as diagnosis, pathogenesis and/or prognosis serum biomarker in SLE and probably LN [16]. *In situ* studies showed that anti-dsDNA were not predominant in renal biopsy samples and they have been estimated to account for no > 10–20% eluted IgG from LN kidneys [17, 18]. Interestingly, anti-dsDNA IgM have been inversely correlated with LN, similar to other self-reactive IgM antibodies such as anti-phospholipid IgM, pointing out the importance of determining the isotype of anti-dsDNA autoantibodies (reviewed in [19]).

Several theories have been proposed to explain the deposition of anti-dsDNA antibodies in renal glomerular tissue of LN patients. The original hypothesis that circulating preformed antibody/DNA complexes could become trapped within the glomerulus is now considered unlikely as it is not supported by the low concentration of circulating ICs and the failure to detect anti-DNA antibodies in these complexes. It has been proposed that anti-dsDNA antibodies could directly cross-react with cell surface antigens or components of the glomerular basement membrane such as α-actinin, α-enolase, annexin A2, laminin or bind to negatively charged matrix components such as heparan sulfate. Although cross-reactivities can be proven *in vitro*, conflicting evidence is available about the potential cross-reactivity of these antibodies *in vivo*. Serum anti-DNA antibodies were found to display less cross-