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Review article

Clinical and pathologic considerations of the qualitative and quantitative aspects of lupus nephritogenic autoantibodies: A comprehensive review

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ABSTRACT

Autoantibodies are key mediators in determining the clinical manifestations of systemic lupus erythematosus (SLE). The mechanisms by which antibodies may be harmful to self tissues encompass complement mediated inflammation, cell apoptosis and immune-complexes mediated damage, however the precise cooperation of antibodies in SLE have not been unravelled so far.

Lupus nephritis (LN) is a protean feature of SLE resulting in wide variety of symptoms including asymptomatic proteinuria, mild renal disease until end-stage renal failure which are triggered by complex autoantibody interactions.

Novel clues concerning development and self-maintenance of LN have come to light in recent times, pointing straight to a multistep inflammatory process which is incited by anti-chromatin antibodies, the best known being anti-DNA and anti-nucleosome antibodies, culminating in a self-maintaining inflammatory loop with spreading of glomerular inflammation. In the maintenance of the inflammatory process pro-inflammatory antibodies are involved, among which anti-C1q are thought to play a major role, whereas hindrance of the nephritic process could be actively mediated by protective autoantibodies.

Despite being so relevant in occurrence of LN, nor anti-chromatin neither anti-C1q antibodies have been precisely characterized in terms of origin, antigen specificity and mechanisms of action.

Moreover, novel autoantibodies are emerging in LN which can modify disease course, whereas the pathogenic value of a myriad of cross-reactive antibodies has been progressively challenged.

The aim of this review is to give a comprehensive view of known and emerging autoantibody reactivities involved in renal inflammation and damage going over their origin, mechanisms of action and interactions in determining LN course.

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1. Introduction

Lupus nephritis (LN) occurs in about 50% of patients affected with systemic lupus erythematosus (SLE) being one of the most threatening manifestations of the disease, encompassing mild renal damage until end-stage renal disease [1–3]. The pathogenesis of LN has not been clarified so far, and firm prognostic serum biomarkers predicting whether a histological LN class would turn into another and how it will affect patient prognosis are still lacking [4–6]. Nevertheless, diverse panels of autoantibodies are being tested which can inform on LN evolution and severity [7–16] yet they are still irksome to handle in common clinical practice.

Among a huge variety of autoantibodies involved in SLE manifestations, LN retains the most extensive group. Since past times, several attempts have been made in order to classify those autoantibodies, according to their pathogenic potential, antigen specificity, or time of appearance during LN [17,18]. In light of current knowledge on LN onset and development, a functional classification appears the most suitable to their connotation.

2. Pathogenic initiating antibodies

2.1. Anti-dsDNA antibodies

Anti-double stranded(ds)DNA antibodies are a well-characterized marker of SLE and are included in SLE classification criteria since 1982 [19,20]. They are present in the large majority of SLE patients and have a well-known correlation with renal involvement [21,22].

However, despite they have been used for a long time both as a follow-up tool and predictors of LN flares [21,23], their target antigens and their origin have not been clear-cut defined.

2.1.1. Anti-dsDNA antibody generation

Birth of anti-dsDNA is fascinating, since the presence of isotype-switched, somatically mutated anti-dsDNA immunoglobulins (Ig)G assumes the occurrence of a T-dependent B cell autoimmune response against nucleic acids, which are not naturally immunogenic.

Two major hypothesis may sustain this apparent paradox, which are likely to cooperate in the priming of naïve T helper (Th) cells.

The first is the hapten-carrier hypothesis [24–26], by which non-immunogenic DNA bound to a T-specific peptide would be able to evoke a T-helped B response. Indeed, because Th cells cannot be activated in a cognate fashion by DNA alone, autoreactive B cells in lymph nodes would internalize circulating DNA bound either to exogenous peptides e.g. bacterial or viral proteins [27] or to endogenous peptides, e.g. histone-derived peptides binding DNA in the form of nucleosomes [28]. B cells would then be able to process the DNA-peptide complex and to present the sole peptide loaded onto Major Histocompatibility Complex (MHC) II molecules to autoreactive dormant T cells in secondary lymphoid organs [29]. Hence, T cells would be primed to recognize the carrier (peptide) that had rendered its hapten (DNA) immunogenic. Activated T cells would then help B cells bearing a DNA-dedicated B cell receptor (BCR) to expand and mature into antibody secreting cells [30]. In this view, both properly reactive (e.g. virus-dedicated) and autoreactive T cells would be able to trigger an autoimmune response leading to production of nephritogenic antibodies.

This is an intriguing hypothesis with a still smoky profile. First, anti-dsDNA antibodies arising following an infectious trigger are unlikely to last enough to incite a durable autoimmune response and a full-blown LN [31–33]; second, histone-specific autoreactive T cells that had escaped central tolerance would have to overcome their peripheral anergy [28,34] in order to light up a secondary response. A unifying theory suggests that foreign antigen-specific T cells would proliferate secreting interleukin (IL)-2 which, in turn, would interrupt the anergic state and sustain the expansion of histone-specific T cells [35]. This theory is supported by the evidence that T cell lines initiated by T antigen-nucleosome complexes respond to pure histones and nucleosomes upon priming [28,36] even though recent evidence has suggested the antibody response in SLE prone individuals following a bacterial infection could be shifted to a response against the phosphodiester backbone, rather than extending the recognition to other types of DNA [24].

One may argue whether histone-specific autoreactive T cells are the sole responsible for anti-dsDNA antibody production. According to the second hypothesis i.e. the autologous-hapten hypothesis on anti-dsDNA generation, B cells are able to present fragments of their own BCR on MHC II molecules, namely endogenous Ig variable-region determinants (IgV), to idiotypic-specific T cells which may in turn help a secondary B-cell response [37,38]. Both previous and recent experimental data in mice have shown that B cells may internalize fragments of complementary determining region (CDR)3 [39–41] or process newly synthesized intracellular Ig and present them to specific T cells in an immunogenic fashion [42] eventually leading to germinal center (GC) formation and isotype switching [37,43,44], provided BCR ligation occurs [43].

Idiotypes can be presented by either B cells or other antigen presenting cells (APC) [37,45–47] through receptor-mediated endocytosis. Evidence of this process was obtained in vitro [42] and remade in both lupus models [37] and nonautoimmune mice [48] which developed lethal autoimmune-driven organ failure when rendered transgenic for Ig L chain and T cell receptor (TCR) [38].

Interestingly, anti-idiotypic specific T cells appear at a growing rate in sera of mice double-transgenic for a Ig L chain and an idiotype-specific TCR as they get older [38], which may be due to the increased rate of BCR maturation and somatic hypermutation resulting in novel idiotypic peptides that are recognized by idiotypic specific T cells escaped from central tolerance.

The fact that such self-antigen presentation may lead to an undisturbed secondary response may be explained by at least three concurring circumstances; i) tolerizing pressure leading to deletion of idiotypic-positive T cells is limited due to the hidden and above all casual nature of the B IgV formation in the bone marrow; ii) activated B cells and/or professional APC present somatically mutated V-region determinants [42] that are broadly unknown to the immune system; iii) heavy chain CDR3 idiotypes of anti-dsDNA antibodies show similarities with both histone-derived and microbial peptides that can trigger cross-reactivity of T cells [41].

Limitation to the in vivo relevance of this mechanism mainly reside in that the real amount of idiotypic-specific T cell clones and the chance of T-B collaboration are reduced under physiological conditions [38], nevertheless it should be taken into account as an