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Elimination of Nucleoproteins in Systemic Lupus Erythematosus and Antinuclear Autoantibodies Production

Andrei S. Trofimenko

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Abstract

The distinctive feature of systemic lupus erythematosus (SLE) is an immune reaction directed to diverse spectrum of autoantigens, which tends to change along with the disease spreading. The most common targets of the autoantibodies are protein and nucleoprotein components of cell nuclei: dsDNA, histones, nucleosomes, Sm antigen, and Ro and La antigens. Considering that the exact causes of this tolerance loss are unknown, a certain number of hypotheses are now discussed. One of the most promising is "waste disposal" concept, which makes a link between broken elimination of cellular debris, mononuclear phagocyte system dysfunction, and initiation of autoimmunity by the antigen presenting cells in SLE. This chapter concerns the ways nuclear antigens release from cells, necrosis, and apoptosis, as well as the key molecular mechanisms of transport and elimination of these antigens, its disturbances in SLE, and connection with innate immunity by mononuclear cells. Special attention is paid to nucleosomes and DNA degradation process, its principal factors (DNase I, C1q, SAP), blood DNA transportation by immune complexes, and immune stimulating action of DNA in SLE. Current pros and cons for the waste disposal concept and existing research trends in this field are discussed.

Keywords: systemic lupus erythematosus, autoantigens, DNA, nucleoproteins, DNase I, antigen cleavage

1. Introduction

Systemic lupus erythematosus (SLE) is a prototypic diffuse autoimmune disease of connective tissue with multiple organ involvement. The history of its exploration is not so long, compared with some other rheumatic diseases, such as osteoarthritis and gout. But, there is

surprisingly few breakthrough advances in its basic conception since the 1950s, when this condition was established as a separate autoimmune disease and glucocorticoids became a groundwork in its treatment. The absence of integral and fully consistent theory of SLE etiopathogenesis appears to be the main problem for researchers, trying to improve the treatment mainly by empirical approach.

SLE etiology and pathogenesis are generally interpreted now as a multifactorially driven autoimmune process [1]. According to this conception, SLE is induced by multiple interactions of immunological, genetic, hormonal, microbial, and environmental factors. Meanwhile, first three ones apparently play the lead [2]. Genetic predisposition to SLE is suggested to be constituted mainly by definite HLA alleles, especially DR2 and DR3, by congenital deficiency of early complement components (C1, C2, C4) and by other genetic associations, including TNF, TCR, IL-6, and other genes [3]. There are genes of C-reactive protein (CRP), C1q, Fcγ-receptors, DNase I, serum amyloid P (SAP), and PDCD1 within seven loci, which are strongly linked with SLE [4]. Moreover, knocking out of these genes in mice induces autoimmune condition with glomerulonephritis [5, 6].

SLE occurs predominantly in women of childbearing age and, to a lesser extent, in prepuberta or menopause, whereupon a contribution of sex hormones could be assumed. Both men and women with SLE have high estrogen levels, the men also have low testosterone and high luteinizing hormone concentrations [7]. The connection between these deviations and SLE could be explained considering their influence on immune system cells, in particular, promotion of B cell proliferation and antibody synthesis under high estrogen levels [8].

Among all the events that can be proposed to initiate SLE onset, the leading one is suggested to be virus infection [9]. Although this "trigger agent" is not definitely identified, a wide spectrum of viruses, including Epstein-Barr virus, retroviruses, and herpesviruses, could make a substantial contribution [10]. Other influencing factors are insolation, drugs, and some pollutants.

The prominent immunological feature of SLE is the production of autoantibodies directed to a wide spectrum of self-antigens. According to Sherer et al. [11], more than 100 autoantigens, which could react with SLE-related antibodies, were mentioned in previously reported researches. However, antibodies to chromatin and its particular elements, nucleosomes, dsDNA, histones, components of DNA replication, and transcription apparatus are most representative for SLE. The second important cluster of antigens involves ribonucleoproteins and its constituents: RNA, small nuclear ribonucleoprotein (snRNP), Sm antigen, and Ro (SS-A) and La (SS-B) antigens. The third group, antiphospholipid antibodies, is common in SLE as well. Anti-DNA antibodies, and specifically anti-double-stranded DNA (dsDNA) antibodies, are thought to have most pathogenetic and diagnostic importance in SLE [12]. Their titers correlate with disease activity, and participation of anti-dsDNA antibodies in lupus nephritis is well established [13, 14].

The realization of anti-dsDNA pathogenic potential can occur by several ways. The most important contribution to systemic inflammation is generally attributed to the formation of immune complexes (IC), with both circulating and tissue-fixed antigens [15]. Nephritogenic action of ICs is mediated primarily by interaction with Fc receptors and Toll-like receptors, and, to a lesser extent, through classical pathway of complement activation [16]. In addition, autoantibodies could interfere in functioning of circulating, membrane, or even intracellular molecules [17].

However, pathogenic action is not an overall feature of anti-DNA antibodies. Both healthy individuals and SLE patients have at least two types of serum anti-DNA antibodies, unrelated directly with autoimmunity. First, there are low affinity antibodies, directed mainly against single-stranded DNA, which can be attributed to natural autoantibodies repertoire [18]. Another type consists of antibodies that are highly specific to microbial single-stranded DNA [19]. The essence of differences, influencing the pathogenic potential of these three types, is given in **Table 1**.

The way pathogenic anti-DNA antibodies appear in SLE is not well established until now. Several conjectures were made for explaining disturbed tolerance to autologous DNA. One of the hypotheses is implication of molecular mimicry, when immune response to autoantigens is induced by exogenous molecules with similar epitopes [24]. Epitope spreading mechanism may also participate in it, subsequently producing antibodies to hidden epitopes after initial reaction to major epitope [25]. Disturbance of T and/or B cellular function is third possible cause of it. Th2-polarization of CD4$^+$ T-cellular response and predominance of Th2-associated cytokines generally distinguish SLE [26]. In addition, there is low content of regulatory CD4$^+$CD25$^+$ T cells that restrict effector functions of CD4$^+$ and CD8$^+$ T cells and diminished suppressor activity of CD8$^+$T cells [27, 28]. Circulating B cells are usually low, mainly due to decrease of resting subpopulations, naïve and memory B cells, being in possible connection with high levels of mature plasmocytes in bone marrow [29]. Causes and mechanisms of the lymphocyte imbalance in SLE are incompletely disclosed now, as well as its pathogenetic relevance.

For the reviewing problem, information about structure of anti-dsDNA V genes, obtained from the mouse models and SLE patients, is of particular importance. Compared to their progenitors, mature genes were found to have multiple somatic hypermutations, which lead to very high avidity of these anti-dsDNA IgG [30]. Increase of arginine, asparagine, and lysine

Factor	Natural autoantibodies	SLE-associated autoantibodies	Antibodies, induced by immunization
Class	Mainly IgM	Mainly IgG	IgM or IgG
Avidity to DNA	Low	Moderate or high	High
Type of DNA to react	Preferentially with ssDNA	Usually both with ssDNA and dsDNA, more rarely—specific to dsDNA	Highly specific to ssDNA
Leading DNA epitope	No data	Deoxyribose-phosphate backbones	Immunogen-specific sequence of bases
Interaction with antigens, other than DNA	With wide spectrum of antigens	With restricted pattern of antigens	Extrinsic
Isotype switching and complement fixation	Extrinsic	Typical	Extrinsic
Somatic mutations of V gene	Few or absent	Typical	Typical
Ability to penetrate cells	In many idiotypes	In particular idiotypes	No data

Table 1. Tentative differences of pathogenic anti-DNA antibodies in SLE [20–23].

in the Complementarity-determining regions (CDR) due to hypermutations results in high isoelectric point of the antibodies, named cationic because of it [31]. Cationic anti-dsDNAs are more nephritogenic apparently through interaction with either negatively charged elements of glomerular basement membrane or DNA-containing antigens *in situ* [32].

Both somatic hypermutations and isotype switching are distinctive features of antigen-dependent B cell selection by T helper cells. High avidity of these autoantibodies points out the similarity of epitopes of the relevant autoantigen to dsDNA. Meanwhile, purified homo-logic DNA have been considered to be poorly immunogenic in health and in SLE models for a long time [33]. In view of this contradiction, there is emerging attention to different classes of endogenous nucleoproteins as anti-dsDNA inductors in SLE.

Besides anti-DNA antibodies, anti-nucleosome antibodies are also attributed to have a special pathogenetic significance in SLE [34]. Priority of anti-nucleosome immune response compared to anti-DNA and anti-histone ones is indirectly confirmed by revelation of earlier subtype of anti-nucleosome antibodies that do not interact with both DNA and histones [35]. There is close association of these antibodies with SLE activity and the kidney involvement [36]. But, unlike anti-dsDNA, anti-nucleosome antibodies do not develop glomerular deposits in the absence of nucleosomal antigens; further perfusion of nucleosome-containing ICs through the kidneys results in appearance of linear immunoglobulin deposits along glomerular base-ment membrane [37]. In addition, after interaction with antinuclear antibodies, nucleosome-containing apoptotic bodies, deposited on glomerular basement membrane or in mesangial space, turn into so-called electron-dense deposits, an attribute of IC-mediated nephritis. There is no immunoglobulin fixation in the kidneys outside these deposits [38].

In most SLE cases, serum anti-dsDNA and anti-nucleosome antibodies are presented at the same time [39]. Furthermore, chromatin immunization induces not only anti-nucleosome but also anti-dsDNA and anti-nucleosome antibodies, possibly through epitope spreading [40]. High avidity of anti-nucleosome antibodies is achieved by the same somatic hypermutations, as for anti-dsDNA production; reversion of these mutations to the initial sequence results in the loss of capability to interact with nucleoproteins and, interestingly, in obtaining antiphos-pholipid activity [41].

Altogether, increasing research data suggest that nucleosomes are just the best candidate anti-gen to induce and/or maintain production of anti-chromatin autoantibodies and to influence pathogenicity of preexisting immunoglobulins. In view of it, efficient elimination of endog-enous nucleoproteins in SLE seems to be an important factor that counteracts the disease spreading.

2. Normal generation and clearance of extracellular DNA

Normal extracellular DNA concentrations are usually quite low, but the values may substan-tially differ depending on the detection approach and contamination of plasma with leukocytic DNA [42]. Circulating DNA is found to be not in free state but mainly as a part of mono- and

oligonucleosomes; this conclusion is based upon its particular molecular weight and binding with histones [43]. Nucleosomes can release from cells during several physiological and pathological processes, namely apoptosis, necrosis, and formation of extracellular traps.

Apoptosis is considered to be predetermined death followed by the removal of damaged or unnecessary cells that is genetically, morphologically, and biochemically standalone of other kinds of cell destruction [44]. An essential condition for normal course of apoptosis is cleavage and utilization of chromosomal DNA. Internucleosomal fragmentation of chromatin is performed by specific apoptotic nucleases during early phase of the process [45]. Nuclear antigens, including nucleosomes, moved then to little bulbs of cell membrane, so-called apoptotic bodies [46]. Interestingly, in some virus infections, endogenous nucleoproteins are bundled together with virions and, thereby, can be jointly presented in apoptotic bodies [47].

The next phase includes transition of aminophospholipids, phosphatidylserine, and phosphatidylethanolamine to external side of cell membrane, and their opsonization by serum proteins, especially by C-reactive protein, C1q, and serum amyloid P (SAP) [48, 49]. This complex becomes a signal to mononuclear phagocytes for recognition and uptake. Interaction of phosphatidylserine and its circulating cofactors (C1q, β_2-glycoprotein I) with C1q receptor and Mer receptor of phosphatidylserine, expressed on macrophage surface, probably plays the lead in this complicated and insufficiently explored process [50, 51]. The ultimate destruction of engulfed nucleoproteins is provided by lysosomal enzymes, primarily by DNase II and cathepsins D, B, and L [52]. This way of clearance, which is supposed to be a major one, allows to keep the continuity of cell membrane as its distinctive feature and, thus, enables to prevent full-scale release of intracellular compounds to interstitial space [53]. Another peculiarity is the production of proinflammatory cytokines (TGF-β and IL-10), inhibiting antigen presentation by dendritic cells [54].

Appearance of circulating oligonucleosomes in apoptosis depends, to a large extent, on the activity of phagocytes [55]. Functional blocking of these cells in mice *in vivo* with clodronate is demonstrated to abolish plasma DNA spike after loading by apoptotic or necrotic cells [56]. Additional factor of substantial influence on DNA release is sex hormone balance, so far as above-mentioned DNA spike is much more higher in female mice compared to males and spays [57]. The causes of partial dissipation of DNA-containing substance during phagocytosis are now unsure. Tentative persistence of apoptotic cells, until their secondary necrosis and membrane disruption begin, is an alternative way of DNA release if elimination potential of mononuclear phagocytes is insufficient.

The second important source of extracellular DNA is cell necrosis. Unlike apoptosis, it is characterized by early cell membrane, proinflammatory effect as a result of different influences, and induction of dendritic cell maturation [58]. In necrosis, DNA is degraded at a later stage compared to apoptosis, with DNase I playing a considerable part in it [59].

The newly discovered and promising phenomenon, characterized by DNA release out of its natural compartment, is a formation of so-called extracellular traps. They were first found in neutrophils, thus being named neutrophil extracellular traps (NETs) [60]. NET are unusual extracellular structures, which are suggested to be a spare defense mechanism, activating

when there are pathogens or particles, too big to be englobed by phagocytes [61]. In this case, large fibers, consisting of chromatin, serve as an external scaffold for immobilized enzymes, antimicrobial peptides, and ion chelators with locally high levels [62]. The components of NET, including dsDNA, histones, nucleosomes, and ribonucleoproteins, become bound to exogenous molecules when NET eliminates its target and thus may obtain new antigenic features.

In general, there is sustained release of nucleoproteins to extracellular space in health, and its rate can be considerably increased under certain conditions. Efficiency of its elimination strongly depends on circulating cofactor molecules, such as C1q, CRP, SAP, as well as DNase I and IgM [63]. They opsonize chromatin and keep it soluble, thus promoting digestion of long chromatin segments, transportation through circulation, and further recognition by macrophages [64]. The terminal points of this transfer are mononuclear phagocyte cells, primarily in the liver and spleen [65]. Overall efficiency of this elimination mechanism is quite high, since after injection of considerable amount of exogenous DNA, or after spontaneous release of endogenous nucleoproteins during hemodialysis, half-life of the DNA in circulation is within 4–15 min [66].

An alternative pathway of DNA elimination, that is just a subsidiary one in the absence of SLE, carries out by means of circulating immune complexes (CIC). Their clearance is determined principally by the activity of complement system. Binding of C1q with CIC results in the restriction of its further growth, prevention of precipitation, and induction of C3b and C4b occurrence [67]. Coupling of these molecules with CIC allows it to interact with CR1 complement receptor (CD35) of red blood cells [68]. Normal CIC transfer to macrophages of the spleen and liver presumably goes on in connection with erythrocytes, probably for prevention of CIC outflow from circulation, and the binding is more tight when CIC contains high molecular DNA (nearly 6000 kDa), then in case of shorter DNA segments (200–600 kDa) [69]. Both CIC and DNA, complexed with circulating opsonins, are captured by macrophages through Fcγ-receptors, the former alongside with CR1 cleavage [70]. However, elimination of DNA by means of CIC is much slower compared to CRP-SAP-linked DNA [71].

Apart from the elimination, binding of circulating ligands with DNA makes an obstacle for access of immune cells to nucleosome etitopes. This is especially important in view of chromatin immunology. It is generally considered that pure extracellular DNA have limited immunogenicity unless CpG motifs [72]. On the contrary, conjugation of protein with oligodeoxyribonucleotide can strongly promote interaction of the protein portion with antigen presenting cells, enhance antibody production, and presumably induce Th2-polarization [73]. From the other side, protein could serve as a carrier for oligonucleotide hapten. Circulating DNA ligands might also interfere in reaction of preexisting autoantibodies with apoptotic debris [74]. In light of all mentioned above, endogenous DNA elimination pathway, especially serum clearance mediators and mononuclear phagocytes, should be regarded in SLE.

3. DNA elimination pathway in SLE

Extracellular DNA levels in SLE patients tend to be appreciably elevated, their circulating DNA have predominantly low molecular weight and contain only human sequences [75]. It

is also almost completely double-stranded and mainly included in oligonucleosomes, linked with serum proteins and immunoglobulins [76]. High plasma DNA concentration is usually associated with SLE flares and vascular involvement, being inversely correlated with anti-dsDNA titers, and decreases after efficient SLE treatment [77].

Functioning of the clearance mediators in SLE has some differences. Increase of disease activity does not generally combine with substantial elevation of plasma SAP and CRP levels; SAP molecular weight as well as its affinity to nucleosomes and heparin are also changeless [78]. Moreover, SAP-linked DNA levels are substantially decreased in SLE, despite elevation of total extracellular DNA; they reversely correlate with anti-dsDNA and disease activity [79]. On the contrary, plasma C1q concentrations tend to be lower in high SLE activity and in lupus nephritis, also directly correlating with CIC-linked DNA levels [80]. These changes taken one with another can be accounted for reallocation of plasma DNA pool to CIC in the presence of high-avidity anti-dsDNA. As C1q binds with both CIC and CRP-SAP-chromatin complex and participates in elimination of every type, simultaneous decrease of C1q and CIC-linked DNA is supposed to be a result of joint tissue deposition [81]. Some evidences were indeed revealed after analysis of DNA-containing CIC in SLE.

Compared to normal individuals, SLE patients commonly have elevated CIC-linked DNA concentration, which further increases along with disease activity, but its decrease is more inherent in extreme SLE flares and overt nephritis [82]. DNA from SLE CIC is double-stranded and mainly consists of fragments, which correspond to oligonucleosomes in their length, 150–250 and 370–460 bp, compared to 20 and 30–40 bp in normal controls [83]. It is revealed in SLE that in this DNA pool CpG motifs are 5–6 times more frequent than in human genome [84]. Apart from DNA and immunoglobulins, SLE CICs contain CRP, C1q, C3b, and C4b [85].

Clearance of CIC is reduced in SLE, and their half-life negatively correlates with SLE activity and extent of lupus nephritis manifestation [86]. This might be due to either impairment of CIC transportation or disturbance of phagocytosis. Furthermore, active SLE is known to have C3/C4 hypocomplementemia and low CR1 on red blood cells, probably because of its consumption [87]. It leads to persistence of CIC mostly out of erythrocytic pool, both free and connected with other blood cells [88]. This circumstance may be the cause of increased uptake of CIC by the liver macrophages and decreased one in the spleen, revealed by injection of labeled ICs to SLE patients [89]. Another unexpected finding from this experiment is substantial reversed release of partially digested ICs outside of phagocytes, which begins 40–60 min after the injection, coinciding with internalization period [90]. The causes and mechanisms of this phenomenon are now unknown. There is single publication about tentative disturbance of interaction between Fcγ receptors and intermediate filaments of mononuclear cells in SLE, what might affect internalization [91]. It is also known that knocking out of Axl/mer/tyro3 tyrosin kinase gene in Mer[kd] mice is followed by disturbance of apoptotic debris internalization together with development of spontaneous autoimmunity. [92].

Delivery of endogenous nucleoproteins to the resident liver and spleen macrophages is thus realized in SLE presumably by way of CIC, while circulating protein mediators are responsible for this function in health. Pathogenetic importance of this shift is not restricted only to extravasation and tissue deposition of "free" DNA-containing CIC. Apart from phagocytosis, contact of CIC with macrophage Fcγ receptors initiates synthesis of proinflammatory signals,

which can induce and maintain autoimmune responses [93]. Conversely, CRP-SAP-linked DNA promotes release of cytokines and chemokines, which suppress inflammation and auto-immunity as well as raise activation threshold of dendritic cells [94].

It is supposed that immune stimulating action of DNA-containing CIC in SLE is mediated by TLR9 Toll-like receptors, together with Fcγ receptors. After CIC internalization by phagocyte, TLR9 move from endoplasmic reticulum to phagosomes and then bind with CpG motifs of DNA-IgG-FcγRII complex [95]. According to the data reported by Lövgren et al. [96] and Means et al. [97], DNA-containing IC obtained from SLE patients promote macrophages and dendritic cells *in vitro* by means of TLR9 to produce α and γ interferons, IL-8, IL-1β, IL-6, IL-18, IL-12p40, TNF, and to generate chemokine signals to peripheral mononuclear cells, immature dendritic cells, T and NK cells. IC derived from patients with rheumatoid arthritis, Sjogren's disease, and DNA-lacking IC from SLE patients does not demonstrate these effects. Treatment of the IC from SLE patients with DNase I makes cytokine and chemokine induction down by 90–100% [98]. One may conclude that abundance of "free" DNA-containing CIC could amplify inflammation in SLE both directly and indirectly.

Using gene knockout approach, a possible relation between disturbance of cell debris removal and autoantibody synthesis is managed to establish. Mice with disabled SAP, C1q, Mer, secreted IgM genes develop spontaneous autoimmune disease with glomerular lesion and production of antinuclear antibodies [99]. This connection could also appear in human SLE.

As follows from the above, additional factors, that could digest extracellular DNA, mainly DNase I, become of special importance in SLE, when ordinary clearance pathway is disabled. Results of DNase I gene knockout had been published in 2000 [100], and since then the enzyme is considered to be a mediator of DNA clearance. Earlier data about low serum DNase I activity in SLE [101, 102] made this factor even more challenging for exploration of immunological tolerance to autologous DNA.

4. The DNase I riddle

DNase I is a DNA-specific endonuclease, which participates in DNA destruction in the presence of Mg^{2+} or Mn^{2+} cations. DNase I is able to destruct single-stranded, double-stranded, and protein-bound DNA; in the latter case, DNA breakdown is performed presumably in segments, free from protein, for example, in internucleosomal connectors of chromatin or in DNA segments where expression is going on [103]. Serum DNase I is usually supposed to be synthesized in gastrointestinal tract, and normal serum nuclease activity is provided almost completely by its function [104]. Proteases enhance DNase I effect on chromatin DNA, possibly due to removal of histones or liberation of basic amino acids, histidine, arginine, and lysine, which are known to be DNase I activators [105]. In general, little is known about physiological DNase I activators, including those, by which serum DNase I activity become significantly increased shortly after injection of purified DNA *in vivo* [106]. G-actin is widely considered to be a predominant physiological DNase I inhibitor [107].

Despite extensive examination, our knowledge about DNase I functions is quite superficial. Its digestive function as a participant of pancreatic secretion is the only universally recognized one. Other possible roles, including apoptotic chromatin degradation, cellular debris removal after necrosis, destruction of DNA genome viruses and some other, need to be fully established [108–110]. An important aspect of DNase I action is the loss of antigenic properties; it can be achieved for nucleoproteins and ICs, both circulating and *in situ* [111].

The rise of interest to DNase I in SLE became after the research performed by Napirei and colleagues had been published [100]. DNase I knockout in mice led to anti-dsDNA production, glomerular IC deposition, and lupus-like glomerulonephritis pathology. SLE patients and NZB/NZW F_1 lupus mice models were found to have low serum DNase I activity [112, 113]. Subsequently, it was shown with some preanalytic corrections that change of serum DNase I activity in SLE was bidirectional, with only about 30% of low enzyme activity, while other patients had moderately increased serum DNase I activity [114].

The origin of these changes is now unknown. The attempt to connect low DNase I activity with high serum actin concentrations was then rejected [114]. Numerous efforts to identify genetic changes, which can influence on the enzyme activity, resulted in very rare incidence of functionally significant gene alterations, about two per 1000 sequenced SLE patients [115–117]. Other important information, provided by geneticists, was markedly increased expression of DNase I gene in SLE [115]. One consistent explanation for it, enhanced DNase I inhibition in SLE, was challenged by Prince and colleagues [118]. Another hypothesis can be the inhibition of DNase I by specific autoantibodies, which were found by Yeh and colleagues [119]. Several factors are more likely to influence DNase I activity in SLE, as it was later shown, with about 50% cases of predominant inhibition by autoantibodies and/or actin, and the other half, impacted by unknown factor [114]. Without extensive research, this riddle is now difficult to solve.

5. Conclusion

If we could try to bring together all the facts, mentioned above, to puzzle them all into a single reasonable explanation, we will inevitably create so-called waste disposal hypothesis first published by Walport [120]. This concept defines that in SLE the most likely source of autoantigens and also leading autoimmunity inductor could be apoptotic bodies on the surface of apoptotic cells, containing almost all characteristic SLE antigens, or, as an alternative, necrotic cell debris. Another obligate condition for autoimmunity induction is postulated to be impaired clearance of the cellular "waste" and, as a consequence, antigen uptake by immature dendritic cells and their activation [121]. Several different impairments of the clearance pathway are proposed to induce SLE. Although this hypothesis seems to be consistent, and accounts for many clinical peculiarities and controversies of SLE, it has some weak points. There is no good inducible SLE model based on this concept. There is no explanation of late SLE onset, especially long after pregnancy, within this theory. The cases of spontaneous remission without glucocorticoid treatment are quite rare, despite obvious variability of "waste" generation rate.

Results of treatment with DNase I are generally discouraging. An enthusiast can, however, object to it that any correct theory usually has multiple discordances at the beginning of its life. So we shall wait a little and collect pros and contras for the final assessment of this hypothesis.

Author details

Andrei S. Trofimenko

Address all correspondence to: a.s.trofimenko@mail.ru

1 Research Institute for Clinical and Experimental Rheumatology, Volgograd, Russia

2 Volgograd State Medical University, Volgograd, Russia

References

[1] Crow MK. Etiology and pathogenesis of systemic lupus erythematosus. In: Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, editors. Kelley and Firestein's Textbook of Rheumatology. 10th ed. Philadelphia: Elsevier; 2017. pp. 1329–1344

[2] Ferretti C, La Cava A. Overview of the pathogenesis of systemic lupus erythematosus. In: Tsokos GC, editor. Systemic Lupus Erythematosus: Basic, Applied and Clinical Aspects. Philadelphia: Elsevier; 2016. pp. 55–62. DOI: 10.1016/B978-0-12-801917-7.00008-5

[3] Deng Y, Tsao BP. Genes and genetics in human systemic lupus erythematosus. In: Tsokos GC, editor. Systemic Lupus Erythematosus: Basic, Applied and Clinical Aspects. Philadelphia: Elsevier; 2016. pp. 69–76. DOI: 10.1016/B978-0-12-801917-7.00010-3

[4] Ceccarelli F, Perricone C, Borgiani P, et al. Genetic factors in systemic lupus erythematosus: Contribution to disease phenotype. Journal of Immunology Research. 2015;**2015**:745647. DOI: 10.1155/2015/745647

[5] Botto M, Dell'Agnola C, Bygrave AE, et al. Homozygous C1q deficiency causes glomerulonephritis associated with multiple apoptotic bodies. Nature Genetics. 1998;**19**(1):56–59. DOI: 10.1038/ng0598-56

[6] Scott RS, McMahon EJ, Pop SM, et al. Phagocytosis and clearance of apoptotic cells is mediated by MER. Nature. 2001;**411**(6834):207–211. DOI: 10.1038/35075603

[7] Zen M, Ghirardello A, Iaccarino L, et al. Hormones, immune response, and pregnancy in healthy women and SLE patients. Swiss Medical Weekly. 2010;**140**(13–14):187–201

[8] Hughes GC, Choubey D. Modulation of autoimmune rheumatic diseases by oestrogen and progesterone. Nature Reviews Rheumatology. 2014;**10**(12):740–751. DOI: 10.1038/nrrheum.2014.144

[9] Nelson P, Rylance P, Roden D, Trela M, Tugnet N. Viruses as potential pathogenic agents in systemic lupus erythematosus. Lupus. 2014;**23**(6):596–605. DOI: 10.1177/09612 03314531637

[10] Ascherio A, Munger KL. EBV and autoimmunity. Current Topics in Microbiology and Immunology. 2015;**390**(1):365–385. DOI: 10.1007/978-3-319-22822-8_15

[11] Sherer Y, Gorstein A, Fritzler MJ, Shoenfeld Y. Autoantibody explosion in systemic lupus erythematosus: More than 100 different antibodies found in SLE patients. Seminars in Arthritis and Rheumatism. 2004;**34**(2):501–537

[12] Ching KH, Burbelo PD, Tipton C, et al. Two major autoantibody clusters in systemic lupus erythematosus. PLoS One. 2012;**7**(2):e32001. DOI: 10.1371/journal.pone.0032001

[13] Gatto M, Iaccarino L, Ghirardello A, et al. Clinical and pathologic considerations of the qualitative and quantitative aspects of lupus nephritogenic autoantibodies: A comprehensive review. Journal of Autoimmunity. 2016;**69**:1–11. DOI: 10.1016/j.jaut.2016.02.003

[14] Floris A, Piga M, Cauli A, Mathieu A. Predictors of flares in systemic lupus erythematosus: Preventive therapeutic intervention based on serial anti-dsDNA antibodies assessment. Analysis of a monocentric cohort and literature review. Autoimmunity Reviews. 2016;**15**(7):656–663. DOI: 10.1016/j.autrev.2016.02.019

[15] Trofimenko AS, Gontar IP, Paramonova OV, Simakova ES, Zborovskaya IA. Experimental modeling of nucleoprotein disposal disorders in systemic lupus erythematosus. Biomeditsinskaya Khimiya. 2015;**61**(5):617–621. [in Russian] DOI: 10.18097/PBMC20156105617

[16] Sjöwall C, Olin AI, Skogh T, et al. C-reactive protein, immunoglobulin G and complement co-localize in renal immune deposits of proliferative lupus nephritis. Autoimmunity. 2013;**46**(3):205–214. DOI: 10.3109/08916934.2013.764992

[17] Song YC, Sun GH, Lee TP, et al. Arginines in the CDR of anti-dsDNA autoantibodies facilitate cell internalization via electrostatic interactions. European Journal of Immunology. 2008;**38**(11):3178–3190. DOI: 10.1002/eji.200838678

[18] Suurmond J, Calise J, Malkiel S, Diamond B. DNA-reactive B cells in lupus. Current Opinion in Immunology. 2016;**43**:1–7. DOI: 10.1016/j.coi.2016.07.002

[19] Haji-Ghassemi O, Müller-Loennies S, Rodriguez T, et al. Structural basis for antibody recognition of lipid A: Insights to polyspecificity toward single-stranded DNA. Journal of Biological Chemistry. 2015;**290**(32):19629–19640. DOI: 10.1074/jbc.M115.657874

[20] Seredkina N, Van Der Vlag J, Berden J, et al. Lupus nephritis: enigmas, conflicting models and an emerging concept. Molecular Medicine. 2013;**19**:161–169. DOI: 10.2119/molmed.2013.00010

[21] Yung S, Chan TM. Mechanisms of kidney injury in lupus nephritis: The role of anti-dsDNA antibodies. Frontiers in Immunology. 2015;**6**:475. DOI: 10.3389/fimmu.2015.00475

[22] Goilav B, Putterman C. The role of anti-DNA antibodies in the development of lupus nephritis: A complementary, or alternative, viewpoint? Seminars in Nephrology. 2015;**35** (5):439–443

[23] Witte T. IgM antibodies against dsDNA in SLE. Clinical Reviews in Allergy & Immunology. 2008;**34**(3):345–347. DOI: 10.1007/s12016-007-8046-x

[24] Aas-Hanssen K, Thompson KM, Bogen B, Munthe LA. Systemic lupus erythematosus: Molecular mimicry between anti-dsDNA CDR3 Idiotype, microbial and self-peptides as antigens for Th cells. Frontiers in Immunology. 2015;**6**:382. DOI: 10.3389/fimmu.2015.00382

[25] Rigante D, Esposito S. Infections and systemic lupus erythematosus: Binding or sparring partners?. International Journal of Molecular Sciences. 2015;**16**(8):17331–17343. DOI: 10.3390/ijms160817331

[26] Talaat RM, Mohamed SF, Bassyouni IH, Raouf AA. Th1/Th2/Th17/Treg cytokine imbalance in systemic lupus erythematosus (SLE) patients: Correlation with disease activity. Cytokine. 2015;**72**(2):146–153. DOI: 10.1016/j.cyto.2014.12.027

[27] Barreto M, Ferreira RC, Lourenço L, et al. Low frequency of CD4+CD25+ Treg in SLE patients: A heritable trait associated with CTLA4 and TGF-beta gene variants. BMC Immunology. 2009;**10**:5. DOI: 10.1186/1471-2172-10-5

[28] Mak A, Kow NY. The pathology of T cells in systemic lupus erythematosus. Journal of Immunology Research. 2014;**2014**:419029. DOI: 10.1155/2014/419029

[29] Zhao L, Ye Y, Zhang X. B cells biology in systemic lupus erythematosus-from bench to bedside. Science China Life Sciences. 2015;**58**(11):1111–1125. DOI: 10.1007/s11427-015-4953-x

[30] Bobeck MJ, Cleary J, Beckingham JA, et al. Effect of somatic mutation on DNA binding properties of anti-DNA autoantibodies. Biopolymers. 2007;**85**(5–6):471–480. DOI: 10.1002/bip.20691

[31] Guo W, Smith D, Aviszus K, et al. Somatic hypermutation as a generator of antinuclear antibodies in a murine model of systemic autoimmunity. Journal of Experimental Medicine. 2010;**207**(10):2225–2237. DOI: 10.1084/jem.20092712

[32] Kohro-Kawata J, Wang P, Kawata Y, et al. Highly cationic anti-DNA antibodies in patients with lupus nephritis analyzed by two-dimensional electrophoresis and immunoblotting. Electrophoresis. 1998;**19**(8–9):1511–1555. DOI: 10.1002/elps.1150190849

[33] Al Arfaj AS, Chowdhary AR, Khalil N, Ali R. Immunogenicity of singlet oxygen modified human DNA: Implications for anti-DNA antibodies in systemic lupus erythematosus. Clinical Immunology. 2007;**124**(1):83–89. DOI: 10.1016/j.clim.2007.03.548

[34] Yap DY, Lai KN. Pathogenesis of renal disease in systemic lupus erythematosus: The role of autoantibodies and lymphocytes subset abnormalities. International Journal of Molecular Sciences. 2015;**16**(4):7917–7931. DOI: 10.3390/ijms16047917

[35] Li T, Prokopec SD, Morrison S, et al. Anti-nucleosome antibodies outperform traditional biomarkers as longitudinal indicators of disease activity in systemic lupus erythematosus. Rheumatology (Oxford). 2015;**54**(3):449–457. DOI: 10.1093/rheumatology/keu326

[36] Bizzaro N, Villalta D, Giavarina D, Tozzoli R. Are anti-nucleosome antibodies a better diagnostic marker than anti-dsDNA antibodies for systemic lupus erythematosus? A systematic review and a study of meta analysis. Autoimmunity Reviews. 2012;**12**(2):97–106. DOI: 10.1016/j.autrev.2012.07.002

[37] Mjelle JE, Rekvig OP, Van Der Vlag J, Fenton KA. Nephritogenic antibodies bind in glomeruli through interaction with exposed chromatin fragments and not with renal cross-reactive antigens. Autoimmunity. 2011;**44**(5):373–383. DOI: 10.3109/08916934.2010.541170

[38] Olin AI, Mörgelin M, Truedsson L, et al. Pathogenic mechanisms in lupus nephritis: Nucleosomes bind aberrant laminin β1 with high affinity and colocalize in the electron-dense deposits. Arthritis & Rheumatology. 2014;**66**(2):397–406. DOI: 10.1002/art.38250

[39] Dieker J, Schlumberger W, McHugh N, et al. Reactivity in ELISA with DNA-loaded nucleosomes in patients with proliferative lupus nephritis. Molecular Immunology. 2015;**68**(1):20–24. DOI: 10.1016/j.molimm.2015.06.004

[40] Voynova EN, Tchorbanov AI, Todorov TA, Vassilev TL. Breaking of tolerance to native DNA in nonautoimmune mice by immunization with natural protein/DNA complexes. Lupus. 2005;**14**(7):543–550

[41] Wellmann U, Letz M, Herrmann M, et al. The evolution of human anti-double-stranded DNA autoantibodies. Proceedings of the National Academy of Sciences USA. 2005;**102**(26):9258–9263. DOI: 10.1073/pnas.0500132102

[42] Thierry AR, El Messaoudi S, Gahan PB, et al. Origins, structures, and functions of circulating DNA in oncology. Cancer and Metastasis Reviews. 2016;**35**(3):347–376

[43] Bryzgunova OE, Laktionov PP. Generation of blood circulating DNA: The sources, peculiarities of circulation and structure. Biomeditsinskaya Khimiya. 2015;**61**(4):409–426. [in Russian] DOI: 10.18097/PBMC20156104409

[44] Reed JC, Green DR, editors. Apoptosis: Physiology and Pathology. Cambridge: Cambridge University Press; 2011. p. 421

[45] Preedy VR, editor. Apoptosis. Enfield: Science Publishers; 2010. p. 654

[46] Yamamoto S, Azuma E, Muramatsu M, et al. Significance of extracellular vesicles: Pathobiological roles in disease. Cell Structure and Function. 2016;**41**(2):137–143

[47] Rosen A, Casciola-Rosen LA, Ahearn J. Novel packages of viral and self-antigens are generated during apoptosis. Journal of Experimental Medicine. 1995;**181**(4):1557–1561

[48] Paidassi H, Tacnet-Delorme P, Arlaud GJ, Frachet P. How phagocytes track down and respond to apoptotic cells. Critical Reviews in Immunology. 2009;**29**(2):111–130

[49] Kinchen JM. A model to die for: Signaling to apoptotic cell removal in worm, fly and mouse. Apoptosis. 2010;**15**(9):998–1006. DOI: 10.1007/s10495-010-0509-5

[50] Peter C, Wesselborg S, Herrmann M, Lauber K. Dangerous attraction: Phagocyte recruitment and danger signals of apoptotic and necrotic cells. Apoptosis. 2010;**15**(9):1007–1028. DOI: 10.1007/s10495-010-0472-1

[51] Biermann MH, Maueröder C, Brauner JM, et al. Surface code – biophysical signals for apoptotic cell clearance. Physical Biology. 2013;**10**(6):065007. DOI: 10.1088/1478-3975/10/6/065007

[52] Kawane K, Nagata S. Nucleases in programmed cell death. Methods in Enzymology. 2008;**442**:271–287. DOI: 10.1016/S0076-6879(08)01414-6

[53] Poon IK, Lucas CD, Rossi AG, Ravichandran KS. Apoptotic cell clearance: Basic biology and therapeutic potential. Nature Reviews Immunology. 2014;**14**(3):166–180. DOI: 10.1038/nri3607

[54] Biermann MH, Veissi S, Maueröder C. The role of dead cell clearance in the etiology and pathogenesis of systemic lupus erythematosus: Dendritic cells as potential targets. Expert Review of Clinical Immunology. 2014;**10**(9):1151–1164. DOI: 10.1586/1744666X.2014.944162

[55] Arandjelovic S, Ravichandran KS. Phagocytosis of apoptotic cells in homeostasis. Nature Immunology. 2015;**16**(9):907–917. DOI: 10.1038/ni.3253

[56] Jiang N, Reich CF 3rd, Pisetsky DS. Role of macrophages in the generation of circulating blood nucleosomes from dead and dying cells. Blood. 2003;**102**(6):2243–2250

[57] Pisetsky DS, Jiang N. The generation of extracellular DNA in SLE: The role of death and sex. Scandinavian Journal of Immunology. 2006;**64**(3):200–204. DOI: 10.1111/j.1365-3083.2006.01822.x

[58] Podolska MJ, Biermann MH, Maueröder C. Inflammatory etiopathogenesis of systemic lupus erythematosus: An update. Journal of Inflammation Research. 2015;**8**:161–171. DOI: 10.2147/JIR.S70325

[59] Krysko DV, D'Herde K, Vandenabeele P. Clearance of apoptotic and necrotic cells and its immunological consequences. Apoptosis. 2006;**11**(10):1709–1726

[60] Brinkmann V, Reichard U, Goosmann C, et al. Neutrophil extracellular traps kill bacteria. Science. 2004;**303**:1532–1535

[61] Zawrotniak M, Rapala-Kozik M. Neutrophil extracellular traps (NETs) - formation and implications. Acta Biochimica Polonica. 2013;**60**(3):277–284

[62] Gupta S, Kaplan MJ. The role of neutrophils and NETosis in autoimmune and renal diseases. Nature Reviews Nephrology. 2016;**12**(7):402–413. DOI: 10.1038/nrneph.2016.71

[63] Park B, Lee J, Moon H, et al. Co-receptors are dispensable for tethering receptor-mediated phagocytosis of apoptotic cells. Cell Death & Disease. 2015;**6**:e1772. DOI: 10.1038/cddis.2015.140

[64] Gregory CD, Pound JD. Microenvironmental influences of apoptosis *in vivo* and *in vitro*. Apoptosis. 2010;**15**(9):1029–1049. DOI: 10.1007/s10495-010-0485-9

[65] Prabagar MG, Do Y, Ryu S, et al. SIGN-R1, a C-type lectin, enhances apoptotic cell clearance through the complement deposition pathway by interacting with C1q in the spleen. Cell Death & Differentiation. 2013;**20**(4):535–545. DOI: 10.1038/cdd.2012.160

[66] Gauthier VJ, Tyler LN, Mannik M. Blood clearance kinetics and liver uptake of mononucleosomes in mice. Journal of Immunology. 1996;**156**(3):1151–1156

[67] Manderson AP, Botto M, Walport MJ. The role of complement in the development of systemic lupus erythematosus. Annual Review of Immunology. 2004;**22**:431–456

[68] Odera M, Otieno W, Adhiambo C, Stoute JA. Dual role of erythrocyte complement receptor type 1 in immune complex-mediated macrophage stimulation: Implications for the pathogenesis of *Plasmodium falciparum* malaria. Clinical & Experimental Immunology. 2011;**166**(2):201–207

[69] Horgan C, Burge J, Crawford L, Taylor RP. The kinetics of ^{3}H-dsDNA/anti-DNA immune complex formation, binding by red blood cells, and release into serum: Effect of DNA molecular weight and conditions of antibody excess. Journal of Immunology. 1984;**133**(4):2079–2084

[70] Karsten CM, Köhl J. The immunoglobulin, IgG Fc receptor and complement triangle in autoimmune diseases. Immunobiology. 2012;**217**(11):1067–1079. DOI: 10.1016/j.imbio.2012.07.015

[71] Rojko JL, Evans MG, Price SA, et al. Formation, clearance, deposition, pathogenicity, and identification of biopharmaceutical-related immune complexes: Review and case studies. Toxicologic Pathology. 2014;**42**(4):725–764. DOI: 10.1177/0192623314526475

[72] Hartmann G. Nucleic Acid Immunity. Advances in Immunology. 2017;**133**:121–169. DOI: 10.1016/bs.ai.2016.11.001

[73] Sano K, Shirota H, Terui T, et al. Oligodeoxynucleotides without CpG motifs work as adjuvant for the induction of Th2 differentiation in a sequence-independent manner. Journal of Immunology. 2003;**170**(5):2367–2373

[74] Squatrito D, Emmi G, Silvestri E, Prisco D, Emmi L. SLE Pathogenesis: From apoptosis to lymphocyte activation. In: Roccatello D, Emmi L, editors. Connective Tissue Disease: A Comprehensive Guide. Vol. 1. Heidelberg: Springer; 2016. pp. 23–34

[75] Chan RW, Jiang P, Peng X, et al. Plasma DNA aberrations in systemic lupus erythematosus revealed by genomic and methylomic sequencing. Proceedings of the National Academy of Sciences of the United States of America . 2014;**111**(49):E5302–E5311. DOI: 10.1073/pnas.1421126111

[76] Chen JA, Meister S, Urbonaviciute V, et al. Sensitive detection of plasma/serum DNA in patients with systemic lupus erythematosus. Autoimmunity. 2007;**40**(4):307–310

[77] Zborovskaya IA, Trofimenko AS, Gontar IP, et al. Prospects of extracorporeal biological therapy of systemic lupus erythematosus using the composite adsorbents. Kremlevskaya medicina. 2013;**3**:85–89 [in Russian]

[78] Firooz N, Albert DA, Wallace DJ, et al. High-sensitivity C-reactive protein and erythrocyte sedimentation rate in systemic lupus erythematosus. Lupus. 2011;**20**(6):588–597

[79] Voss A, Nielsen EH, Svehag SE, Junker P. Serum amyloid P component-DNA complexes are decreased in systemic lupus erythematosus: Inverse association with anti-dsDNA antibodies. Journal of Rheumatology. 2008;**35**(4):625–630

[80] Fenton K. The effect of cell death in the initiation of lupus nephritis. Clinical & Experimental Immunology. 2015;**179**(1):11–16. DOI: 10.1111/cei.12417

[81] Truedsson L, Bengtsson AA, Sturfelt G. Complement deficiencies and systemic lupus erythematosus. Autoimmunity. 2007;**40**(8):560–566. DOI: 10.1080/08916930701510673

[82] Nezlin R. A quantitative approach to the determination of antigen in immune complexes. Journal of Immunological Methods. 2000;**237**(1–2):1–17

[83] Nezlin R, Alarcón-Segovia D, Shoenfeld Y. Immunochemical determination of DNA in immune complexes present in the circulation of patients with systemic lupus erythematosus. Journal of Autoimmunity. 1998;**11**(5):489–493. DOI: 10.1006/jaut.1998.0231

[84] Sano H, Takai O, Harata N, et al. Binding properties of human anti-DNA antibodies to cloned human DNA fragments. Scandinavian Journal of Immunology. 1989;**30**(1):51–63

[85] Pradhan V, Rajadhyaksha A, Mahant G, et al. Anti-C1q antibodies and their association with complement components in Indian systemic lupus erythematosus patients. Indian Journal of Nephrology. 2012;**22**(5):353–357. DOI: 10.4103/0971-4065.103911

[86] Kavai M, Szegedi G. Immune complex clearance by monocytes and macrophages in systemic lupus erythematosus. Autoimmunity Reviews. 2007;**6**(7):497–502

[87] Julkunen H, Ekblom-Kullberg S, Miettinen A. Nonrenal and renal activity of systemic lupus erythematosus: A comparison of two anti-C1q and five anti-dsDNA assays and complement C3 and C4. Rheumatology International. 2012;**32**(8):2445–2451. DOI: 10.1007/s00296-011-1962-3

[88] Elkon KB, Santer DM. Complement, interferon and lupus. Current Opinion in Immunology. 2012;**24**(6):665–670. DOI: 10.1016/j.coi.2012.08.004

[89] Davies KA, Peters AM, Beynon HL, Walport MJ. Immune complex processing in patients with systemic lupus erythematosus. *In vivo* imaging and clearance studies. Journal of Clinical Investigation. 1992;**90**(5):2075–2083. DOI: 10.1172/JCI116090

[90] Davies KA, Robson MG, Peters AM, et al. Defective Fc-dependent processing of immune complexes in patients with systemic lupus erythematosus. Arthritis & Rheumatology. 2002;**46**(4):1028–1038

[91] Vázquez-Doval J, Sánchez-Ibarrola A. Defective mononuclear phagocyte function in systemic lupus erythematosus: Relationship of FcRII (CD32) with intermediate cytoskeletal filaments. Journal of Investigational Allergology and Clinical Immunology. 1993;**3**(2):86–91

[92] Jung JY, Suh CH. Incomplete clearance of apoptotic cells in systemic lupus erythematosus: Pathogenic role and potential biomarker. International Journal of Rheumatic Diseases. 2015;18(3):294–303. DOI: 10.1111/1756-185X.12568

[93] Toong C, Adelstein S, Phan TG. Clearing the complexity: Immune complexes and their treatment in lupus nephritis. International Journal of Nephrology and Renovascular Disease. 2011;4:17–28

[94] Rekvig OP, Van der Vlag J. The pathogenesis and diagnosis of systemic lupus erythematosus: Still not resolved. Seminars in Immunopathology. 2014;36(3):301–311. DOI: 10.1007/s00281-014-0428-6

[95] Tsokos GC, Lo MS, Reis PC, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. Nature Reviews Rheumatology. 2016;12(12):716–730. DOI: 10.1038/nrrheum.2016.186

[96] Lövgren T, Eloranta ML, Båve U, et al. Induction of interferon-alpha production in plasmacytoid dendritic cells by immune complexes containing nucleic acid released by necrotic or late apoptotic cells and lupus IgG. Arthritis & Rheumatology. 2004;50 (6):1861–1872

[97] Means TK, Latz E, Hayashi F, et al. Human lupus autoantibody-DNA complexes activate DCs through cooperation of CD32 and TLR9. Journal of Clinical Investigation. 2005;115(2):407–417

[98] Liao X, Reihl AM, Luo XM. Breakdown of immune tolerance in systemic lupus erythematosus by dendritic cells. Journal of Immunology Research. 2016;2016:6269157. DOI: 10.1155/2016/6269157

[99] Guo Y, Orme J, Mohan C. A genopedia of lupus genes - lessons from gene knockouts. Current Rheumatology Reviews. 2013;9(2):90–99

[100] Napirei M, Karsunky H, Zevnik B, et al. Features of systemic lupus erythematosus in Dnase1-deficient mice. Nature Genetics. 2000;25(2):177–181. DOI: 10.1038/76032

[101] Frost PG, Lachmann PJ. The relationship of desoxyribonuclease inhibitor levels in human sera to the occurrence of antinuclear antibodies. Clinical & Experimental Immunology. 1968;3(5):447–455

[102] Chitrabamrung S, Rubin RL, Tan EM. Serum deoxyribonuclease I and clinical activity in systemic lupus erythematosus. Rheumatology International. 1981;1(2):55–60

[103] Zborovskaya IA, Trofimenko AS, Gontar IP. Anti-DNase I antibody response in systemic lupus erythematosus: A possible way of the enzyme dysfunction. Nauchno Prakticheskaya Revmatologiya. 2007;**45**:64–68. [in Russian] DOI: 10.14412/1995-4484-2007-3

[104]   Fujihara J, Yasuda T, Ueki M, et al. Comparative biochemical properties of vertebrate deoxyribonuclease I. Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology. 2012;163(3–4):263–273. DOI: 10.1016/j.cbpb.2012.07.002

[105]   Shapot VS. Nucleases. Moscow: Meditsina Publishers; 1968. p. 212 [in Russian]

[106]   Mazurik VK, Moskaliova EU. Aspartate carbamoyltransferase, DNA polymerase, and DNase activities in rat hemopoietic tissues after single DNA injection. Bulletin of Experimental Biology and Medicine. 1974;77(2):32–35 [in Russian]

[107]   Yokota E. Isolation of actin and actin-binding proteins. Methods in Molecular Biology. 2017;1511:291–299. DOI: 10.1007/978-1-4939-6533-5_23

[108]   Nikiforov ND, Mamontov SG, Ilnitsky Yu A, et al. Treatment of acute hepatitis B with deoxyribonuclease. Sovetskaia Meditsina. 1990;7:82–83 [in Russian]

[109]   Peer V, Abu Hamad R, Berman S, Efrati S. Renoprotective effects of DNAse-I treatment in a rat model of ischemia/reperfusion-induced acute kidney injury. American Journal of Nephrology. 2016;43(3):195–205. DOI: 10.1159/000445546

[110]   Koyama R, Arai T, Kijima M, et al. DNase γ, DNase I and caspase-activated DNase cooperate to degrade dead cells. Genes to Cells. 2016;21(11):1150–1163. DOI: 10.1111/gtc.12433

[111]   Lefkowith JB, Kiehl M, Rubenstein J, et al. Heterogeneity and clinical significance of glomerular-binding antibodies in systemic lupus erythematosus. Journal of Clinical Investigation. 1996;98(6):1373–1380

[112]   Macanovic M, Lachmann PJ. Measurement of deoxyribonuclease I (DNase) in the serum and urine of systemic lupus erythematosus (SLE)-prone NZB/NZW mice by a new radial enzyme diffusion assay. Clinical & Experimental Immunology. 1997;108(2):220–226

[113]   Sallai K, Nagy E, Derfalvy B, et al. Antinucleosome antibodies and decreased deoxyribonuclease activity in sera of patients with systemic lupus erythematosus. Clinical and Diagnostic Laboratory Immunology. 2005;12(1):56–59. DOI: 10.1128/CDLI.12.1.56-59.2005

[114]   Trofimenko AS, Gontar IP, Zborovsky AB, Paramonova OV. Anti-DNase I antibodies in systemic lupus erythematosus: Diagnostic value and share in the enzyme inhibition. Rheumatology International. 2016;36(4):521–529. DOI: 10.1007/s00296-016-3437-z

[115]   Feng XB, Shen N, Qian J, et al. Single nucleotide polymorphisms of deoxyribonuclease I and their expression in Chinese systemic lupus erythematosus patients. Chinese Medical Journal (England). 2004;**117**(11):1670–1676

[116]   Yasutomo K, Horiuchi T, Kagami S, et al. Mutation of DNASE1 in people with systemic lupus erythematosus. Nature Genetics. 2001;28(4):313–314. DOI: 10.1038/91070

[117] Bodaño A, González A, Ferreiros-Vidal I, et al. Association of a non-synonymous single-nucleotide polymorphism of DNASEI with SLE susceptibility. Rheumatology (Oxford). 2006;45(7):819–823. DOI: 10.1093/rheumatology/kel019

[118] Prince WS, Baker DL, Dodge AH, et al. Pharmacodynamics of recombinant human DNase I in serum. Clinical & Experimental Immunology. 1998;113(2):289–296

[119] Yeh TM, Chang HC, Liang CC, et al. Deoxyribonuclease-inhibitory antibodies in systemic lupus erythematosus. Journal of Biomedical Science. 2003;10(5):544–551

[120] Walport MJ. Complement and systemic lupus erythematosus. Arthritis Research. 2002;4(Suppl 3):S279–S293. DOI: 10.1186/ar586

[121] Mahajan A, Herrmann M, Muñoz LE. Clearance deficiency and cell death pathways: A model for the pathogenesis of SLE. Frontiers in Immunology. 2016;7:35. DOI: 10.3389/fimmu.2016.00035