murine and human systemic lupus erythematosus (SLE, lupus) is characterized by the appearance of autoantibodies directed to nuclear and cell membrane phospholipid components. Some functionally related nucleic-acid-containing macromolecules such as chromatin or ribonucleoprotein particles are specifically targeted both by autoantibodies and T cells involved in lupus pathogenesis. In the last decade, the identification of target structures has strongly improved diagnostic tools. Furthermore, characterization of autoantigens has provided insight into pathogenic mechanisms to understand why these autoantigens are recognized in SLE. However, the recognition of autoantigens and a stable immune response towards these specificities requires the coincidence of several events (such as environmental triggers in the external world) plus abnormalities in genetically susceptible organisms that modify normal immune responses. Furthermore, the persistence of the autoantibody response in lupus long after the initial trigger suggests that endogenous autoantigens (from the internal world) are important in sustaining the ongoing immune response. Once the critical threshold is breached, there is a failure of the immune system to down-regulate normal immune responses which thus become abnormal and persistently autoreactive [1].

The importance of different events and genes that initiate and/or maintain the autoimmune response may vary from patient to patient, all resulting in the characteristic autoimmune features and pathology of this systemic autoimmune disease.

Among the different autoantigenic candidates that are recognized by autoantibodies in SLE, there are only two nuclear antigens that are considered pathognomonic of SLE, double-stranded DNA (dsDNA) and the Sm antigens of the U-1 small nuclear ribonucleoprotein complex [2]. Antibodies to these autoantigens are sufficiently discriminating to be part of the American College of Rheumatology (ACR) classification criteria for SLE [3]. In addition, antibodies to phospholipids are included in the ACR criteria, although they are less specific for the disease. Therefore, the following review will focus on these key nuclear autoantigens in SLE, their role as diagnostic targets and the current concepts of how they become targets of the immune system. The identification of responses to these early autoantigenic epitopes might offer new therapeutic implications in SLE, such as induction of specific tolerance.

The external world—infections and autoantigens (molecular mimicry)

Among the different triggers, there is growing evidence for infections as an initial event triggering lupus-specific autoimmune responses. Bacterial or viral infections may induce a non-specific stimulus of the innate immune system to promote activation and expansion of autoreactive T and B cells. Table 1 gives an overview of potential triggering agents in SLE.

In recent years, there has been growing evidence for a role of Epstein-Barr virus (EBV) infections as an initial trigger for SLE. Independent case studies have reported the onset of lupus either concurrently or immediately following infection with EBV [4, 5]. Epidemiological studies have demonstrated a higher incidence of EBV infection and higher levels of antibodies to EBV proteins in both young and adult lupus patients compared with matched normal individuals [6, 7]. Patients with SLE have an abnormally elevated Epstein-Barr virus load in their blood [8]. The importance of EBV infection is also indicated by animal studies. Expression of the Epstein-Barr virus nuclear antigen-1 (EBNA-1) in the mouse can elicit the production of anti-dsDNA and anti-Sm antibodies, but without pathology [9].

There is considerable evidence for molecular mimicry between EBV and regions of the Sm nucleoprotein recognized by autoantibodies from many SLE patients. A proline-rich epitope PPGMRPP in the C-terminus of the ribonucleoprotein SmB/B1 is similar to an epitope in EBNA-1 [10, 11]. Furthermore, the N-terminal 35–58 sequence of the EBNA-1 molecule encoded by EBV is highly homologous to the C-terminal 95–119 region of the SmD1 ribonucleoprotein. This peptide is also cross-reactive with a homologous region of SmD3 [12]. An antigenic domain of the virus-encoded nuclear antigen EBNA-2 also revealed a high degree of homology to the C-terminal peptide 101–119 of the SmD1 protein [13].

Antibodies to EBNA-1 are detected in several autoimmune diseases, but only SLE sera contain antiviral antibodies cross-reactive with the autoantigen [14]. In our recent studies on animal lupus models, immunization of healthy mouse strains with SmD1 83–119 that is highly homologous to the EBNA-1 peptide 35–58 resulted in the generation of anti-Sm and anti-dsDNA antibodies and proteinuria (manuscript in preparation).

Recently, a peptide derived from the 60 kDa Ro ribonucleoprotein [amino acids (aa) 169–180] was identified as an initial autoantigenic epitope for some lupus patients positive for anti-Ro60 antibodies. Despite missing homology, this initial epitope directly cross-reacts with the peptide aa 58–72 from the latent viral protein EBNA-1, again suggesting a role of EBV infection in SLE [15]. Supporting this hypothesis, prior to clinical onset of SLE, some lupus patients developed an autoimmune response to 60 kDa Ro antigen that directly cross-reacts with a peptide from the latent viral protein EBNA-1 [15, 16].

Bacterial infections have also been suspected as a triggering factor for lupus and the induction of anti-dsDNA antibodies in healthy mouse strains based on studies of immunization with...
bacterial DNA [17]. Bacterial DNA, but also viral DNA, differs from vertebrate DNA in the decreased frequency of methylation of CpG dinucleotides. SLE patients have higher levels of circulating plasma DNA enriched in hypomethylated CpGs. Furthermore, SLE patients have hypomethylated genomic DNA (summarized by Krieg [18]). These CpG motifs can induce a variety of immune effects such as polyclonal activation of B cells, secretion of interleukin-6 (IL-6), and resistance to apoptosis that could influence the survival of autoreactive cells [18, 19]. Furthermore, CpG can bind Toll-like receptors (TLR), including TLR9, and activate innate immunity, which can in turn activate acquired immunity to generate IgG antibodies to dsDNA [20]. CpG DNA induces an immunoglobulin (IgG) class switch DNA recombination by activating human B cells through an innate pathway that requires TLR9 and cooperates with IL-10 [21], as discussed in the following section.

Role of innate immune system in SLE—new insights from the discovery of Toll-like receptors

Microbial products can stimulate B cells directly by engaging several members of the TLR family that are specifically designed to detect single- and double-stranded nucleic acids [22]. The 11 known members of the TLR family recognize different antigenic triggers. Among them, TLR9 binds CpG motifs from both bacterial and viral DNA [23]. TLR7 can act as a sensor of viral infections by binding single-stranded viral RNA [24]. Studies further suggested that messenger RNA (mRNA) and nuclear ribonucleoproteins (RNA/protein particles) additionally engage TLR3 and probably further receptors [25].

Protein–nucleic acid complexes such as chromatin–IgG complexes activate antigen-presenting cells by co-engaging B-cell receptor (BCR) and TLR suggesting a role for innate signalling in systemic autoimmunity [26]. Interestingly, immune complexes that contain IgG bound to chromatin activate dendritic cells (DC) more effectively than complexes that contain foreign proteins [25]. Therefore, TLR-mediated immune activation could bridge exogenous and endogenous activation of antigen-presenting cells. As a result of DC activation, a signal cascade is initiated leading to the expression of pro-inflammatory cytokines such as IFN-α, a key player in SLE. Furthermore, DC activation by these immune complexes increases B-cell survival and up-regulates MHC class I and II antigen presentation driving the adaptive immune system [25, 26].

DsDNA-specific B cells could play a decisive role in the activation of autoreactive T cells. As suggested by our in vitro experiments, such B cells could initially be activated in a T cell-independent manner (e.g. by cross-linkage of surface antigen receptors by nucleic acids) and activation of Toll-like receptors [27]. The engagement of TLR would also explain that both T-cell dependent and T-cell independent autoantibody isotypes occur in lupus [28].

Abnormal TLR-mediated cytokine production for IL-10 was detected in lupus-prone mice that could account for a number of immune abnormalities observed in lupus such as increased B-cell survival, chronic activation, hypergammaglobulinemia, and autoantibody production. Furthermore, this B-cell cytokine expression could modify the function of autoreactive T cells [29].

B cells from lupus mice show a very low threshold for stimulation with different CpG motifs [30] and an abnormal response to some CpG sequences, resulting in the up-regulated expression of co-stimulatory molecules and in an increased IgM response compared with control B cells. Chronic administration of CpG oligodeoxynucleotides caused more severe kidney disease in both MRL/lpr mice and NZB/W lupus-prone mice [31, 32]. These data suggest an involvement of TLR-mediated stimulation in lupus pathogenesis. On the other hand, lupus-prone mice immunized with bacterial DNA lived longer [33], and TLR9−/− MRL/lpr knock-out mice have a phenotype similar to the wild type suggesting that TLR9-mediated pathways are not directly involved in lupus pathogenesis in this model [34].

Therefore, the role of TLR9 in lupus pathogenesis in vivo appears controversial and is now under investigation [29]. One study in Korean patients showed that TLR9 gene polymorphisms were not significantly associated with susceptibility to SLE and related phenotypes [35]. It is likely that other TLRs (TLR7, TLR3) might be involved in lupus pathogenesis and this also could explain the preference to react with RNA-binding proteins in lupus.

The key autoantigens as targets of the immune response in lupus

High-affinity antibodies to dsDNA are characteristic hallmarks of human and murine systemic lupus erythematosus. Some subgroups of these antibodies cause renal and vascular injury. Anti-dsDNA antibodies are detected in 30–60% of the SLE sera; 60–83% of lupus patients will be positive for anti-dsDNA antibodies some time during the course of disease (Table 2) [36]. However, the presence of high levels of anti-dsDNA antibodies in the serum does not always correlate with renal disease, and some patients develop nephritis even when serum anti-dsDNA antibodies are absent [37]. These data and others have suggested that anti-dsDNA antibodies are heterogeneous, are not always harmful, and that antibodies with other specificities can cause lupus nephritis [38, 39].

The antigenic stimulus driving the production of anti-dsDNA antibodies in SLE remains elusive [40], but current data provide some strong candidates. Autoantigens specifically detected in

<table>
<thead>
<tr>
<th>Infectious agents</th>
<th>Induces autoantibodies against</th>
<th>Lupus symptoms</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyoma virus</td>
<td>Histones, DNA</td>
<td>Not analysed</td>
<td>90</td>
</tr>
<tr>
<td>EBNA-1 and EBNA-2 of EBV</td>
<td>SmD, SmB’, B, ANA, dsDNA</td>
<td>Not induced</td>
<td>9</td>
</tr>
<tr>
<td>Pneumococcal cell wall polysaccharide</td>
<td>dsDNA</td>
<td>Kidney immune complex deposits</td>
<td>28</td>
</tr>
<tr>
<td>HIV</td>
<td>U1RNAP, Sm, Ro, La, ribosomal P, cardiolipin</td>
<td>Case reports</td>
<td>91</td>
</tr>
<tr>
<td>HIV-1 p24gag</td>
<td>SmB’/B</td>
<td>Not analysed</td>
<td>92, 93</td>
</tr>
<tr>
<td>Bacterial DNA</td>
<td>dsDNA, ssDNA</td>
<td>Improvement</td>
<td>17</td>
</tr>
<tr>
<td>Trypanosoma cruzi, Pseudomonas, Candida albicans, Leishmania, Bartonella</td>
<td>Ribosomal P</td>
<td>Not analysed</td>
<td>94</td>
</tr>
</tbody>
</table>

Table 1. Infectious agents that show the capability to induce autoantibodies towards lupus autoantigens
SLE are mostly macromolecules with proteins and nucleic acid constituents (ribonucleoproteins) such as the snRNP, Ro, La, Sm, nucleosomes or ribosomes [41]. Autoimmune response towards DNA or RNA characteristic for SLE requires T-cell help for the production of high-affinity antibodies, and these nucleic acids are poor or not immunogenic. Therefore, it is now widely accepted that DNA-binding protein in complex with DNA is necessary to break tolerance to DNA [42]. One possible explanation is that some peptides can mimic the anti-dsDNA epitope and can activate T cells to provide help for the generation of anti-dsDNA autoantibodies [40, 43]. Another possible explanation is that a hapten-carrier like mechanism, in which T cells specific for peptides originating from the DNA-binding proteins (such as histones) provides help to DNA-specific B cells for the production of antibodies. This is suggested by studies showing that antibodies to DNA, particularly those that cause damage, are more readily induced by immunization of animals with DNA–protein complexes than by immunization with protein-free DNA [42].

However, the fact that most autoantigens in SLE are ribonucleoproteins suggests that anti-dsDNA antibodies could result during the autoantibody response towards the protein constituent of these autoantigens. The characteristic features of most autoantigenic epitopes in SLE, i.e. location near the nucleic binding sites and a sharing of positive charges, support this.

Indeed, there is growing evidence that the immune response towards dsDNA is primarily directed against ribonucleoproteins such as nucleosomes or small nuclear ribonucleoproteins (snRNPs).

### TABLE 2. Autoantibody reactivity against ribonucleoproteins and their ribonucleosomal epitopes in sera from SLE-patients

<table>
<thead>
<tr>
<th>Macromolecule</th>
<th>Natural peptide</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>dsDNA</td>
<td>Telomere</td>
<td>29–69</td>
<td>66–96</td>
<td>95</td>
</tr>
<tr>
<td>dsDNA</td>
<td>SmD1 83–119</td>
<td>60</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>Nucleosome</td>
<td>45–56</td>
<td>85–95</td>
<td>54, 96</td>
<td></td>
</tr>
<tr>
<td>Nucleosome</td>
<td>Histone</td>
<td>15</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Nucleosomes</td>
<td>Histone 1</td>
<td>45</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>Sm core proteins</td>
<td>SmD3</td>
<td>7–41</td>
<td>93–100</td>
<td>98</td>
</tr>
<tr>
<td>Sm</td>
<td>SmD3</td>
<td>12</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Sm/U1RNP</td>
<td>SmB/B</td>
<td>54.4</td>
<td>Not detected</td>
<td>100</td>
</tr>
<tr>
<td>Sm</td>
<td>SmD183–119</td>
<td>70</td>
<td>93.7</td>
<td>52, 53</td>
</tr>
<tr>
<td>RNP</td>
<td>3–46</td>
<td>25–99</td>
<td>98</td>
<td></td>
</tr>
</tbody>
</table>

Nucleosomes as targets of the autoantibody immune response

Nucleosomes are released from the nucleus into the cytoplasm of dying cells undergoing apoptosis. They are composed of a core particle with a tetramer of two molecules of histones H3 and H4 in the centre, flanked by two dimers of histones H2A–H2B. Two superhelical turns of DNA are wound around this histone octamer [44]. There is growing evidence that nucleosomes constitute one of the primary inciting antigens in SLE [45]. In studies of lupus mice [46] nucleosome autoantibodies occurred early in life, before emergence of anti-dsDNA and antihistone antibodies.

By means of serum adsorption, this nucleosome reactivity was proven to be distinct from anti-dsDNA or antihistone antibodies. Several epitopes are recognized by nucleosome antibodies. Nucleosome-specific monoclonal antibodies that were isolated from young, pre-autoimmune lupus-prone mice had characteristics of multicolonality and recognized a variety of nucleosome epitopes. Probably, many nucleosome-reactive B-cell clones are recruited at the onset of autoimmune response [47]. In most studies, the nucleosome was the most reactive substrate in patients who had SLE (31–88%) compared with antibodies to dsDNA (21–82%). In contrast to anti-dsDNA antibodies, antinucleosome activity is often detected in 25–62% of patients with inactive SLE.

Sm autoantigens of the small nuclear ribonucleoprotein

The Sm autoantigens of the small nuclear ribonucleoprotein (snRNP) are also important autoantigens in lupus. Seven core proteins, B, D1, D2, D3, E, F and G, shared by the majority of the snRNP particles, form a heptamer ring approximately 20 nm in diameter, with the snRNA passing through the centre. The Sm epitopes are distributed on the outside surface of the ring. By using overlapping octapeptides spanning the full length of the B/B protein, the epitope PPPGMRPP, which occurs three times C-terminus of SmB/B, seems to be an important autoantigen [10]. Analysing the immune response towards the SmB/B protein in animal models or in some SLE patients, this linear peptide is recognized very early and spreads to other snRNP autoantigens including U1-specific RNP epitopes frequently targeted by antibodies present in patients with mixed connective tissue disease [10]. By these data, initial immune responses towards linear epitopes and further spreading to linear epitopes can be studied. However, the recognition of conformational epitopes that are detected by autoantibodies in systemic autoimmune diseases [48] is not reflected by these studies and, therefore, the results do not ultimately reflect the immune response *in vivo*.

In contrast to the SmB/B proteins, the SmD polypeptides are regarded as the Sm antigens that are most specific to SLE [49]. The glycine–arginine (GR)-rich carboxyl region of SmD1 is recognized by virtually all Sm-precipitin positive lupus sera [50]. The sequence also shares striking homology to a portion of SmD3 protein. The C-terminus of SmD1 also contains symmetrical dimethylarginines present in the SmD1, D3 and B/B polypeptides targeted exclusively by SLE sera [51]. As detected in experiments by our group, 70% of lupus sera showed reactivity to a conformational epitope within the C-terminus of SmD1 that contains an 8-fold repeat of a GR motif that is involved in nucleic acid binding [52, 53]. Only a minority of these patients has a reactivity to the whole recombinant Sm protein used in most studies to detect anti-Sm antibodies. Presence of these anti-SmD183–119 antibodies has a specificity of 93% for SLE. In the same lupus sera, antinucleosome antibodies were detectable in only 56% of patients [54]. The levels of the anti-SmD183–119 strongly correlate (as did antinucleosome) to disease activity. Levels of anti-dsDNA and anti-SmD183–119 were strongly associated with lupus nephritis [52, 55].

Anti-SmD183–119 antibodies occur in NZB/W mice and MRL/lpr suggesting a pivotal role in the immune response in lupus. Anti-SmD183–119 antibodies are detected at a very early age of 6–8 weeks in the MRL/lpr mouse strain (unpublished observation). Table 2 provides an overview about the role of autoantigens as target for lupus-specific autoantibodies and, therefore, as marker for disease.

Finally, a recent study of patients with SLE with sera stored before onset of disease [16] showed that 77% of patients had autoantibodies for several years before the onset of symptoms. Therefore, development of disease may require more than the ability to make autoantibodies, or the antibodies may have to reach a certain quantity or have a certain specificity, antigen avidity, cross-reactivity and/or charge to cause disease. In that study, the earliest-appearing antibodies were non-specific.
antinuclear antibodies (ANA) and antibodies to Ro(SSA) and La (SSB), then anti-dsDNA and antiphospholipid, and shortly before disease onset anti-Sm and anti-RNP. These data suggest that the response to self expands over time and involves increasing numbers of antigens, and that various antigenic responses can promote the development of T and B cells that recognize new autoantigens, as we have discussed for the SmD1 peptide.

**Apoptosis and detective clearance and lupus autoantigens**

In 1994, Casiola-Rosen et al. [56] reported that nucleosomes and snRNP, including the Sm antigens, become clustered and concentrated in and on surface blebs of cells undergoing physiological apoptosis. During apoptosis, post-translational protein modifications include proteolysis, phosphorylation, oxidation, transglutaminase activation or exposure to mercury. This may lead to the availability of modified (cryptic) antigens for which T and B cells have not been tolerized [45]. Post-translational modifications during apoptosis have been shown for snRNP and spliceosomes [56]. However, the role of post-translational modifications in the antichromatin response in lupus remains to be defined [45]. Nevertheless, evidence has now accumulated to suggest that the cell surface of apoptotic cells contains antigens that are immunogenic in lupus. Thus, immunization of normal mice with apoptotic Jurkat cells raised antibodies that targeted multiple antigens and antigen complexes, including Ku, rRNP, snRNP and vimentin [57]. Injection of syngeneic apoptotic cells or apoptotic thymocytes that are coated with β2-glycoprotein I into normal mice elicited in vivo production of anti-ssDNA and antiphospholipid autoantibodies, but not full-blown disease [58].

It has been suggested by many investigators that apoptosis-derived autoantigens might represent initial epitopes that trigger the production of autoantibodies [59]. Many abnormalities of apoptosis have been described in lupus; however, the nature of the apoptotic defects in SLE needs to be defined further. Some defects described in lupus may represent a result, rather than a cause, of the disease [45]. Therefore, a direct causal link between apoptosis and SLE remains to be established, despite strong evidence that disturbances in cell apoptosis exist in lupus.

Increased apoptosis can also be observed in other chronic inflammatory diseases, including some autoimmune diseases, but high-affinity autoantibodies to snRNP or chromatin do not occur. Therefore, it is more likely that additive and functionally related pathogenic mechanisms are required to boost the effects of apoptosis. Apoptotic clearance defects represent another important pathway that may lead to the development of autoimmunity. Evidence exists to suggest that clearance of apoptotic material is impaired in lupus as a result of primary (genetic) and/or secondary (via antibodies or antigens?) effects [45]. Macrophages from patients with SLE had defects in the phagocytosis of apoptotic cells [60]. Defective clearance of apoptotic bodies was also observed in Clq−/− mice (Clq coating of apoptotic bodies may be required for normal clearance), but this was not detected in other lupus animal models [61, 62].

Several other factors that are linked to lupus pathogenesis can also influence apoptosis. Apoptosis is also stimulated by oestrogens [63]. Furthermore, apoptosis is induced by ultraviolet light [64] and autoantibodies themselves, when they appear in disease, may affect apoptosis positively or negatively [65]. Infections, as discussed before, are important triggers for apoptosis. Autoantigens and viral antigens can co-cluster in the same apoptotic body and could induce the presentation of cross-reactive peptides and initiate an autoimmune response [66].

**T-cell help and expansion of the antisol response by spreading**

T cells specific for autoantigens were detected in SLE patients and in healthy individuals with identical T-cell receptors, suggesting that T-cell autoimmunity to nucleosomes may be a latent property of the normal immune system [67]. To date, in lupus mice and patients, T-cell epitopes in histones and snRNP have been identified by testing different peptides for their ability to stimulate autoreactive T cells *ex vivo*.

Autoepitopes for pathogenic T cells of human and murine lupus were localized at positions 10–33 of histone H2B, aa16–39 and aa71–94 of histone H4 and positions 85–102 of histone H3 [68]. Region 53–85 of H3 seems to contain important T helper (Th) cell epitopes in the NZB/W mouse model and in lupus patients [69].

Several T-cell epitopes were also detected on the SmD1 protein, the SmB/B protein, and in the 70-U1RNP, but there are only few Sm T-cell epitopes detected in both murine lupus and SLE [70]. Our group has identified T cells recognizing the SmD183–119 peptide in both human and murine lupus. In human SLE, the detection of SmD183–119-reactive T cells was associated with cardiopulmonary pathology [27, 71].

T cells provide help for the generation of specific auto antibodies. Furthermore, it is now widely believed that diversification of antibody response results from both T- and B-cell epitope spreading, which is preceded by the initiation of immunity to a single or few self components (Table 3) [68, 72, 73]. Epitope spreading involves the acquired recognition of new epitopes within the same self molecule as well as epitopes residing in proteins that are associated in the same macromolecular complex (intermolecular epitope spreading), such as nucleosomes, spliceosomes and ribosomes [70]. In the prevalent view of the mechanisms involved in epitope spreading, Th cells play a central role [70].

It was demonstrated that a single lupus nucleosome-specific Th clone can provide help to dsDNA, histone-, or nucleosomesspecific B cells which result in intermolecular help and cognate interaction between B and nucleosome-specific T cells [74]. As shown by Th clones, this also occurs in human lupus [75]. The presence of cross-reactive T cells is crucial for the initiation and amplification of specific T-cell help for the production of specific antibodies.

The SmB/B protein is the major antigen followed by the D1 and D2 proteins. A single T-cell epitope generated from one protein in the snRNP particle can support the production of a large family of antibodies that recognize multiple determinants on the snRNP particles [41]. Our group has recently identified SmD183–119-reactive T cells that provide T-cell help for pathogenic anti-dsDNA antibodies in murine lupus. Therefore, it is now evident that nucleosomes as well as peptides from Table 3. Examples of epitope spreading in animal models after immunization with autoantigenic peptides

<table>
<thead>
<tr>
<th>Immunogen</th>
<th>Autoimmune response</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ro 60 (aa 316–335)</td>
<td>Ro60, La, Sm, U1RNP</td>
<td>76</td>
</tr>
<tr>
<td>SmD1 protein</td>
<td>A-RNP, SmD</td>
<td>76</td>
</tr>
<tr>
<td>SmB protein</td>
<td>A-RNP, SmD</td>
<td>76</td>
</tr>
<tr>
<td>SmD183–119</td>
<td>SmD, dsDNA</td>
<td>27, 101</td>
</tr>
<tr>
<td>SmB’/β PPGMRPP</td>
<td>SmD, 70k- A-U1RNP</td>
<td>10</td>
</tr>
<tr>
<td>Murine La (aa 13–30)</td>
<td>Ro52</td>
<td>102</td>
</tr>
<tr>
<td>A2/B1 hRNP (aa 50–70)</td>
<td>hRNP</td>
<td>103</td>
</tr>
<tr>
<td>Nucleosome</td>
<td>dsDNA, nucleosome, histone</td>
<td>104</td>
</tr>
<tr>
<td>(lupus-prone mice)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>La (aa 13–30)</td>
<td>La, Ro</td>
<td>102</td>
</tr>
<tr>
<td>Histone H1</td>
<td>H2, ssDNA</td>
<td>105</td>
</tr>
</tbody>
</table>
snRNP provide T-cell help for the generation of anti-dsDNA antibodies.

Recently, immunization studies with the Ro60 peptide 316–335 have induced antibodies to Ro60, La and snRNP proteins including SmD, suggesting epitope spreading to unrelated macromolecules [76].

Despite the cross-reactivity of T cells, B cells are also involved in the diversification of antibodies. Somatic mutations to arginine residues affect the binding of human monoclonal antibodies to DNA, histones and SmD antigens [77]. Both T- and B-cell spreading can be investigated by following the immune responses to defined autoantigens. However, only a few investigators have also induced lupus symptoms and not just autoantibodies.

One of the antigen groups that promotes cross-talk between T and B cells making pathogenic autoantibodies is located in the VH region of the autoantibodies themselves. We and others have shown that several 12-mer and 15-mer amino acid sequences located in various regions of the VH are T-cell epitopes in NZB/W mice [78, 79]. These peptides occur primarily in autoantibodies in murine Ig. Furthermore, when T cells are cultured with those peptides, they help B cells make IgG anti-dsDNA. Pre-morbid mice immunized with the peptides make anti-DNA earlier than normal, develop nephritis earlier and have significantly shortened survival. Some of the peptides can induce anti-DNA and proteinuria when administered as immunogens to normal mice. Most importantly, a combination of the wild VH peptide administered intravenously as a high-dose tolerogen to NZB/W females can dramatically delay the appearance of autoantibodies and nephritis and prolong life [80]. An artificial peptide designed to be enriched in amino acids recognized by murine T cells in the context of I-Ed is particularly effective in treating murine lupus [81]. Patients with SLE have very similar sequences in similar locations in the VH of their anti-DNA [82]. It is likely that among the genes that predispose to SLE are some that drive selection of B cells with these particular sequences in their surface Ig receptors. Higher proportions of patients with SLE, compared with healthy matched controls, have T cells activated by these VH peptides [82]. The peptides stimulate release primarily of IL-10 and interferon-gamma (IFN-γ) [82]. The importance of these VH peptide self-antigens is that they promote T-cell help for autoantibody production, and their manipulation can improve disease by several mechanisms, including deletion of helper T cells and induction of regulatory T cells that shut off autoreactivity. A VH peptide from human anti-DNA is currently in Phase I trials in induction of regulatory T cells that shut off autoimmunity. With the rediscovery of regulatory T cells and the ongoing progress in studying the role of these cells in SLE, autoantigens can probably also be used to generate autoantigen-specific regulatory T cells as therapeutic interventions. Such approaches would decrease the risk of flares, as it was also shown in MS patients who were tolerized with peptides that were therapeutic in murine lupus.

The authors have declared no conflicts of interest.

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55. Mohan C, Adams S, Stanik V, Datta SK. Nucleosomal

54. McMurray RW, Suwannaroj S, Ndebele K, Jenkins JK. Differential


52. Singh RR, Hahn BH, Tsao BP, Ebling FM. Evidence for

51. McMurray RW, Suwannaroj S, Ndebele K, Jenkins JK. Differential


45. Kaliyaperumal A, Mohan C, Wu W, Datta SK. Nucleosomal

44. McMurray RW, Suwannaroj S, Ndebele K, Jenkins JK. Differential


42. Singh RR, Hahn BH, Tsao BP, Ebling FM. Evidence for

41. McMurray RW, Suwannaroj S, Ndebele K, Jenkins JK. Differential


37. Mohan C, Adams S, Stanik V, Datta SK. Nucleosomal


34. McMurray RW, Suwannaroj S, Ndebele K, Jenkins JK. Differential


32. Singh RR, Hahn BH, Tsao BP, Ebling FM. Evidence for

31. McMurray RW, Suwannaroj S, Ndebele K, Jenkins JK. Differential


29. McMurray RW, Suwannaroj S, Ndebele K, Jenkins JK. Differential


