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REVIEW

Immune Response and Production of Abzymes in Patients with Autoimmune and Neurodegenerative Diseases

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Abstract—The mechanisms of development of autoimmune, neurological, and viral diseases and the possibilities of immune response to various antigens in these pathologies still pose many questions. Human immune system is theoretically capable of synthesizing about a million antibodies with very different properties against the same antigen. It remains unclear how many antibodies and with what properties can form in healthy people and patients with autoimmune diseases (AIDs). The capabilities of traditional approaches, such as enzyme immunoassay or affinity chromatography of Abs on specific sorbents, in answering these questions and analyzing the diversity of antibodies formed against external and internal antigens, as well as their role in the pathogenesis of various diseases, are very limited. Analysis of monoclonal antibodies in the blood of patients with systemic lupus erythematosus (SLE) using phage display revealed that the number of autoantibodies against DNA and myelin basic protein (MBP) can exceed 3-4 thousand, and approximately 30-40% of them are abzymes capable of hydrolyzing DNA and MBP. However, this approach does not allow to investigate the variety of properties of such antibodies, in particular their catalytic activity. Abzymes can play either positive or negative role in the development of various diseases. For example, in HIV-infected patients, abzymes against viral polymerase and integrase cleave these proteins, thus slowing down the development of immunodeficiency syndrome. Other antibodies play a negative role in the pathogenesis of viral, neurological, and autoimmune diseases. Thus, antibodies capable of hydrolyzing DNA and histones can penetrate through the cellular and nuclear membranes, stimulate cell apoptosis, and, as a result, trigger autoimmune processes in many pathologies. Antibodies against MBP cleave this protein in the membranes of cells in nerve tissues, leading to the development of multiple sclerosis (MS). In this case, abzymes against individual histones were able to hydrolyze each of these histones, as well as MBP, while Abs against MBP hydrolyzed MBP and all five histones. It has also been established that the substrate specificity of abzymes in the hydrolysis of histones and MBP varied greatly depending on the stage of MS or SLE development. Here, we used this example to analyze in detail the role that abzymes against various antigens play in their expanded involvement in the pathogenesis of some AIDs. The review also describes the impact of defects in the bone marrow stem cell differentiation characteristic of AIDs in the formation of B lymphocytes producing harmful abzymes and summarizes for the first time the data on the exceptional diversity of autoantibodies and abzymes, their unusual biological functions, and involvement in the pathogenesis of autoimmune pathologies.

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Abbreviations: Ab, antibody; Abz, abzyme; AGD, antigenic determinant; AID, autoimmune disease; MBP, myelin basic protein; MOG, myelinoligodendrocyte glycoprotein; MS, multiple sclerosis; SLE, systemic lupus erythematosus.

INTRODUCTION

Antibodies (Abs) are traditionally described as proteins produced by the immune system and capable of specific binding of antigens. In this classical concept, Abs are similar to enzymes in their ability to specifically interact with antigens, although they are unable to catalyze chemical reactions. This statement is true for most Abs; however, it has been found unexpectedly that Abs can have a catalytic activity. Linus Pauling (1946) suggested that the active sites of enzymes have the maximum complementarity not to the substrates, but rather to the transition states of catalyzed chemical reaction. In this case, the antigen recognition sites in catalytic antibodies should be maximally adapted to the structure of the transition state [1]. However, formation of Abs against very short-lived transition states is impossible. Later, Jencks (1969) hypothesized that catalytically active Abs can be obtained against stable analogs of transition states of chemical reactions [2]. This idea was realized in experimental immunology much later – the methods for production of enzymatically active monoclonal Abs against chemically stable analogs were first described in 1985 [3]. The first catalytically active monoclonal Abs were obtained against *p*-nitrophenyl phosphorylcholine [4] and monoaryl phosphonate esters [5, 6] and were named abzymes (AntiBody enZYMES; Abzs) [4-27]. To date, about 200 artificial Abzs have been described, most of which are specific monoclonal Abs that had been developed as potential drugs. The development of Abzs for medical purposes have been described in several reviews [28-36].

Biological fluids of healthy donors contain various autoantibodies (autoAbs) at low concentrations [37-56]. However, in patients with autoimmune diseases (AIDs) [37-46], neurological pathologies, and viral and bacterial infections [47-57], the concentrations of these Abs are significantly higher. Beside the *typical* autoAbs that are catalytically inactive, up to 30-40% of autoAbs *against specific antigens* can exhibit the enzymatic activity [58-63]. Abzs have been found in biological fluids of patients with many AIDs, as well as neurological, viral, and bacterial diseases [58-63].

The development of AIDs is characterized by spontaneous or antigen-stimulated production of Abs against peptides, proteins, DNA, RNA, their complexes, nucleotides, polysaccharides, etc. [28-36, 56-63]. The origin of natural Abzs against "self" molecules in mammals is a complex process. Similar to artificial Abzs, they can be specific to various enzyme substrates that act as haptens [28-36, 56-63]. Some haptens can change their conformation after forming complexes with high-molecular components (proteins, nucleic acids, polysaccharides, and their associations) and simulate the transition states of respective substrates in the enzyme-catalyzed reactions. AID development is also accompanied by the formation of catalytically active anti-idiotypic Abzs against the active sites of enzymes [64-66]. Natural Abzs with various activities identified in human and mammalian body fluids have been described in [21-36, 56-63].

The presence of Abzs capable of hydrolyzing antigens can be considered as the earliest and reliable marker of initial stages of AIDs [58-63]. Abzs are detected already at the early stages of AIDs and neurological disorders, when the typical markers of these pathologies are yet absent and protein content in the urine and autoAb titers are still within the range characteristic of conditionally healthy individuals. Detection of Abzs is a much more sensitive technique compared to measuring autoAb titers by enzyme immunoassay (EIA), because catalysis results in a significant accumulation of reaction products, which allows detection of even small amounts of Abzs with low but reliably tested activities. For example, anti-DNA Abs have been found at high concentrations (compared to healthy donors) in only 17-18% patients with multiple sclerosis (MS) and 38% patients with systemic lupus erythematosus (SLE) [67], while DNA-hydrolyzing Abs have been detected in ~90-95% patients with MS [68] and SLE [69]. This is due to the fact that the titers of autoAbs in AID patients increase only at the late disease stages or during disease exacerbation. Therefore, we believe that reliably detected presence of Abzs can be considered as an indicator of early stages of pathologies associated with the impaired immune status. At the same time, a dramatic increase in the Abzs activity occurs only after reaching severe stages of AIDs [58-63].

Conditionally healthy people typically lack Abzs [58-63]. However, it was found that the blood of some conditionally healthy donors contained low-active autoAbzs that hydrolyzed polysaccharides [70], thyroglobulin [71-73], and vasoactive neuropeptide [74]. DNA-hydrolyzing Abzs were detected in patients with SLE [68, 69, 75, 76], MS [68, 69], Hashimoto's thyroiditis [77], diabetes mellitus [78], viral hepatitis [79], schizophrenia [80], and HIV (human immunodeficiency virus) infection [81]. The blood of patients with SLE [68, 69, 82, 83], MS [69, 82], viral hepatitis [78], and schizophrenia [84] contained Abzs capable of cleaving RNA and microRNAs. IgGs efficiently hydrolyzing myelin basic protein (MBP) were found in the blood of patients with SLE [85], MS [86, 87], schizophrenia [88], and HIV infection [89]. The blood of patients with sepsis contained Abs with a broad proteolytic activity [90]; Abzs with the aldolase activity were found in some AID patients [91]; Abzs in patients with hemophilia A hydrolyzed factor VIII [92]; Abzs from human milk efficiently cleaved DNA and proteins [93].

Abs capable of cleaving all five histones (H1, H2A, H2B, H3, and H4) were identified in the blood of patients with MS [94], schizophrenia [95], and HIV infection [96]. The blood of healthy humans and animals contained Abzs with the redox functions [97-102]; however, the activity of such antibodies in patients with AIDs and neurological disorders was found to be significantly higher [103].

MECHANISMS OF PROGRESSION OF AUTOIMMUNE DISEASES

To develop new approaches to treating patients with autoimmune and neurological diseases, it is important to understand the mechanisms and causes underlying the emergence and development of such disorders. As has been shown in [58-63, 104-109], the major trigger of autoimmune processes in AIDs, neurological disorders, and viral and bacterial infections is impaired differentiation of bone marrow stem cells (BMSCs).

According to the unitarian theory of hematopoiesis postulated by A. A. Maximov, there are four classes of hematopoietic cells [110]. All blood cells originate from the polypotent stem cells of bone marrow. A stem cell divides with the formation of two new cells, one of which maintains the properties of a stem cell and the other can differentiate into any blood cell without exception. The four major types of hemopoietic precursors of blood cells are:

1. Early erythroid colonies (BFU-Es, erythroid burst-forming units);

2. Granulocytic–macrophagic colonies (CFU-GMs, granulocytic–macrophagic colony-forming units);

3. Later erythroid colonies (CFU-Es, erythroid burst-forming units);

4. Granulocytic–erythroid–megakaryocytic–macrophagic colonies (CFU-GEMMs, granulocytic–erythroid–megakaryocytic–macrophagic colony-forming units).

Bone marrow also contains T and B cells, which are the products of differentiation of hemopoietic cell.

In healthy people, the four types of hemopoietic cells, as well as T and B cells, are formed at a certain ratio. During AID progression, various “non-self” and “self” antigens penetrate through the blood–brain barrier, resulting in the disturbance in the ratio between the six types of cells, i.e., in the impaired differentiation profile of stem cells [58-63, 104-109]. This leads to the formation of new types of cells, including B cells producing antibodies with various properties, in particular, pathological Abzs. Cell differentiation occurs in several stages, so some B cells acquire the ability to synthesize Abzs already in the cerebrospinal fluid, while other cells undergo further differentiation in the blood and organs of humans and animals.

The synthesis of Abzs by specific B cells occurs already in the bone marrow [58-63, 104-109, 111-113]. Abzs from the cerebrospinal fluid of MS patients hydrolyzed DNA, MBP, and oligosaccharides ~30-60 times more efficiently than Abzs from the blood of the same patients [111-113]. Four types of bone marrow cells enter the blood and transform into the cells of human blood and various organs, where cells that have not finally differentiated in the cerebrospinal fluid can undergo further differentiation when exposed to exogenous and endogenous antigens. Impaired differentiation of BMSCs leads to a dramatic activation of lymphocyte proliferation in various organs, including blood, bone marrow, spleen, thymus, and lymph nodes [58-63, 104-109], where additional synthesis of Abzs with various catalytic functions and properties takes place.

B lymphocytes synthesizing harmful Abz can be produced in healthy individuals [114], but these cells are eliminated by apoptosis. In AID patients, apoptosis of lymphocytes is inhibited [58-63, 104-109], resulting in increased proliferation of cells producing harmful antibodies, including Abzs.

Therefore, progression of AIDs is determined mainly by the impaired differentiation of BMSCs, activation of lymphocyte proliferation in organs, and suppression of apoptosis. An important role in AID development belongs to Abzs hydrolyzing blood, cell, and tissue components.

When analyzing the mechanisms of AID development, one should take into account another very important factor. If canonical enzymes are synthesized according to the “one gene – one enzyme” principle, Abs are formed by an absolutely different mechanism, namely, the V(D)J recombination that produces unique DNA sequences encoding variable domains of Abs. The variable regions of heavy (H) and light (L) chains are encoded by the locus divided into several gene segments designated as V (variable), D (diverse), and J (joining) [115]. Activation by an antigen results in rapid proliferation of B cells. Loci encoding hypervariable domains of heavy and light chains are characterized by an increased frequency of point mutations and deletions (the so-called somatic hypermutation). As a result, the daughter cells formed by cell division will produce antibodies with different variable domains. Therefore, somatic hypermutation is another mechanism that increases the diversity of Abs, thus influencing the affinity of these Abs to antigens [116, 117]. The number of B cells synthesizing Abs with different properties, including Abzs against the same antigen, can be very large. Theoretically, human immune system can produce about a million of B lymphocytes secreting antibodies with different properties against the same antigen [118]. In view of this, the potential diversity of the Abz active site structure compared

to classical enzymes is of great interest. It would also be interesting to know how many different Abs, including Abzs, can be formed in mammals with AIDs and neurological disorders and to decipher the biological functions of these Abs.

DIVERSITY OF ABZYMES WITH THE DNase AND RNase ACTIVITIES

An exceptional diversity of polyclonal Abzs with the DNase and RNase activities in the blood of patients with AIDs and neurological pathologies ([39, 58-63, 68, 69, 77-84] and references within), AID-prone mice [119], and healthy animals immunized with DNA, RNA, RNase A, DNase I, and DNase II ([58-63, 68] and references within) has been demonstrated using affinity chromatography of polyclonal IgGs on DNA-cellulose in a NaCl concentration gradient (0.05-3.0 M). IgGs with the DNase activity were distributed over the entire chromatographic profile, including Abs eluted with 3.0 M $MgCl_2$ and acidic buffer (pH 2.6), which destroys strong immune complexes [39, 58-63, 68, 69, 77-84, 119]. It is known that classical DNases typically have only one pH optimum [120, 121]. The fractions with different affinity to DNA-cellulose demonstrated several pH optima and isoelectric points (pI from 4.5 to 9.0), as well as dependence (or lack of it) on different metal ions, such as Mg^{2+}, Mn^{2+}, Ca^{2+}, Co^{2+}, Ni^{2+} ([39, 58-63, 68, 69, 77-84] and references within).

It has been shown that the active sites of Abzs are located in the variable regions of light chains, while variable regions of heavy chains increase the affinity of Abs for antigens [58-63, 94-96, 106-109].

A potential number of Abzs with the DNase activity in the blood of SLE patients was estimated for the kappa-type Ab monoclonal light chains (MLCs) that were obtained using a phage library containing 10^6 variants of light chains [122, 123]. The pool of phage particles was divided into 11 peaks, all of which contained MLCs that efficiently hydrolyzed DNA. Individual colonies were obtained using phage particles eluted from DNA cellulose with 0.5 M NaCl and acidic buffer (pH 2.6). Forty-five colonies were randomly selected from 451 individual colonies eluted with 0.5 M NaCl, and 15 of them (~33%) efficiently hydrolyzed DNA [122]. Among 33 colonies selected out of 687 individual colonies eluted with the acidic buffer (peak 11), 19 (58%) exhibited the DNase activity [123]. The resulting 34 MLC preparations efficiently cleaved DNA, but differed in the relative activity, dependence on metal ions, and optimal pH values [122, 123]. The affinity of obtained MLCs for DNA was approximately 2 to 3 orders higher than the affinity of DNase I (K_M, 46-58 μM) [124]. The average content of Abzs with the DNase activity among 78 colonies isolated from two out of 11 analyzed peaks was 43.6%. Out of 1138 colonies grown on two Petri dishes, approximately 496 colonies contained cells producing Abzs with the DNase activity. The total number of different MLCs with the DNase activity in 11 peaks was estimated as ~2000-3000 [122, 123]. It was shown that anti-DNA Abzs from the sera of patients with SLE can have absolutely different properties corresponding to canonical DNase I and DNase II: they can either depend or not on DNA sequences ([39, 58-63, 68, 69, 77-84] and references within).

IgGs with the RNase activity capable of hydrolyzing homopolynucleotides, cCMP, and yeast RNA were identified in the sera of patients with SLE [69, 82, 83], MS [68], Hashimoto's thyreoiditis, polyarthritis [82], schizophrenia [84], and different types of hepatitis [79]. Similar to DNA-cleaving Abs, Abs with the RNase activity were separated into a large number of fractions by affinity chromatography. The fractions differed in the pH optimum values, specificity toward RNA and microRNAs, and dependence (or lack of it) on metal ions [58-63, 69, 79, 82-84]. The activity of the obtained Abzs strongly depended on the substrate used and disease under study; the highest RNase activity was observed for Abzs from patients with MS and SLE [58-63, 68, 69, 82, 83]. Some IgGs were found to hydrolyze various microRNAs in a site-specific manner. The average activity of IgGs in patients with SLE, MS, and schizophrenia was significantly higher (22.3 to 84.8-fold) than in conditionally healthy donors [82-84].

DIVERSITY OF ABZYMES WITH THE PROTEOLYTIC ACTIVITY

Abzs with the proteolytic activity have been found in patients with some autoimmune, neurological, and viral diseases. An exceptional diversity of these Abzs has been demonstrated by the affinity chromatography of polyclonal Abs on sorbents with the corresponding immobilized proteins [85, 125, 126]. Chromatography on MBP–Sepharose showed that catalytically active Abs distributed over the entire elution profile [85, 125, 126]. IgGs of all four subclasses (IgG1-4) were able to hydrolyze MBP [85, 126]. The contribution of Abs of each subclass to the total activity was individual for each patient and disease, as well as for the type of proteolytic activity. Proteolytically active total IgG and IgM preparations mainly contained Abs with the serine proteases-like activity [58-63].

HIV is a causative agent of acquired immunodeficiency syndrome (AIDS), one of the most dangerous human diseases. Retroviruses (including HIV) cause chronic infections in humans. During the virus life cycle, viral DNA is integrated into the host genome

with the involvement of HIV enzyme integrase [127, 128]. Abzs from the blood serum of HIV-infected patients demonstrated an extreme diversity in the hydrolysis of viral reverse transcriptase and integrase [58-63].

The first discovered Abs with the serine protease-like and metal-dependent proteolytic activities were IgGs from patients with MS [86, 129] and SLE [130]. Quite unexpected results were obtained in the analysis of proteolytic activity of integrase-hydrolyzing IgGs and IgMs from HIV-infected patients ([58-63, 131] and references within). Along with inhibitors of serine and metal-dependent proteases, the activity of these Abzs was strongly suppressed by inhibitors of acidic and thiol proteases. However, for five IgG preparations and seven IgM preparations, the total effect of specific inhibitors against these four classes of proteases was over 100%, indicating that the immune system of HIV-infected patients produced anti-integrase Abzs with active sites that contained amino acid residues typical of four different classes of proteases: acidic, thiol, serine, and metalloproteases [58-63, 131].

All IgG preparations isolated from the serum of 32 HIV-infected patients cleaved all five human histones (H1, H2A, H2B, H3, and H4) [132], but their significantly varied between IgGs from different patients. IgGs from the blood of 40% healthy donors also hydrolyzed five histones, although ~16 to 20 times less efficiently compared to Abzs from the blood of HIV-infected patients [132]. The ability of Abs to cleave histones was suppressed by specific inhibitors of metal-dependent and serine proteases and, unexpectedly, by inhibitors of thiol proteases. These findings suggested that the immune system of HIV-infected patients synthesized a variety of antibodies with different catalytic properties, which was confirmed by the analysis of monoclonal Abzs with the proteolytic activity.

Using the same library of kappa-type light chains, MLCs capable of hydrolyzing MBP were obtained and homogeneous MLC samples were analyzed [133-136] using the same approaches as in the analysis of MLCs with the DNase activity [122, 123]. The pool of phage particles was separated into ten fractions with different affinities for MBP. All fractions efficiently hydrolyzed MBP. The fraction eluted from MBP–Sepharose with 0.5 M NaCl solution was used to isolate individual colonies [133-136]. Seventy-two colonies were randomly selected out of 440 individual colonies; 22 out of the selected colonies (~30%) demonstrated the MBP-hydrolyzing activity. These MLC preparations were purified by chromatography on a Ni^{2+}-HiTrapTM sorbent, followed by high-performance gel filtration. All 22 isolated MLC preparations hydrolyzed MBP with different efficiency [133-136]. Unexpectedly, 12 out of 22 MLC preparations exhibited a metalloprotease activity, which was inhibited only by ethylenediaminetetraacetate (EDTA). Four MLC preparations had the serine protease-like activity, as they were inhibited by phenylmethylsulfonyl fluoride (PMSF) only. For three MLC preparations, the effects of PMSF and EDTA were comparable (~40% and 60%, respectively). The activity of three other MLCs was strongly suppressed by iodoacetamide, a specific inhibitor of thiol proteases. Interestingly, iodoacetamide significantly inhibited the activity of MLCs that were also inhibited by EDTA, which suggests that two MLCs were chimeric antibodies with their active sites typical of thiol proteases and metalloproteases. Very unexpectedly, the activity of one MLC preparation was inhibited by EDTA, PMSF, and iodoacetamide, the total effect of three inhibitors being 154%, i.e., active site of this MLC combined amino acid residues characteristic of three types of classical proteases. All described MLCs differed in the optimal pH values and ability to be activated by metal ions (Ca^{2+}, Mg^{2+}, Co^{2+}, Zn^{2+}, Ni^{2+}, and Mn^{2+}).

Unexpected results were also obtained in the analysis of three MLC preparations: NGTA1-Me-pro, NGTA2-Me-pro-Tr, and NGTA3-pro-DNase [133-136]. DNA sequences encoding these three MLCs were analyzed and proved to be very similar (88-100% identity) to the embryonic lines of IgLV8 light chain genes of several antibodies described in literature [133-136].

NGTA1-Me-pro was a metalloprotease inhibited only by EDTA [134]. In the presence of different metal ions, its activity toward MBP decreased in the following order: $Ca^{2+}>Mg^{2+}>Ni^{2+}\approx Zn^{2+}\approx Co^{2+}\approx Mn^{2+}>Cu^{2+}$.

NGTA1-Me-pro demonstrated two different pH optima: 6.0 and 8.5. The optimal concentration of $CaCl_2$ was 6.0 mM at pH 6.0 and 1.0 mM at pH 8.5. The K_M value for MBP (20.0 ± 2.0 μM) and k_{cat} at pH 6.0 (0.22 ± 0.02 min^{-1}) were different from those at pH 8.5 (40.0 ± 3.0 μM and 0.07 ± 0.005 min^{-1}, respectively), which clearly indicates that NGTA1-Me-pro had two different metal-dependent activities within the same active site [134].

NGTA2-Me-pro-Tr was specifically inhibited by PMSF (42%) and EDTA (58%). i.e., exhibited the properties of chimeric protease with serine and metal-dependent activities [135]. After the treatment with PMSF, the pH optimum for its metalloprotease activity was 6.5-6.6; after dialysis vs. EDTA, the pH optimum for its serine protease-like activity was 7.4-7.5. At pH 7.5, the K_M value was 9.0 ± 1.0 μM (for MBP) and k_{cat} was 8.0 ± 0.6 min^{-1}; at pH 6.5 (in the presence of $CaCl_2$), the affinity for MBP decreased (K_M, 24.0 ± 2.0 μM) and the reaction rate increased (k_{cat}, 15.2 ± 1.1 min^{-1}) [135]. NGTA2-Me-pro-Tr was the first example of Abzs with the active site combining serine protease-like and metalloprotease activities [135].

It should be emphasized that all recombinant MLCs were obtained by the same technique [133-136].

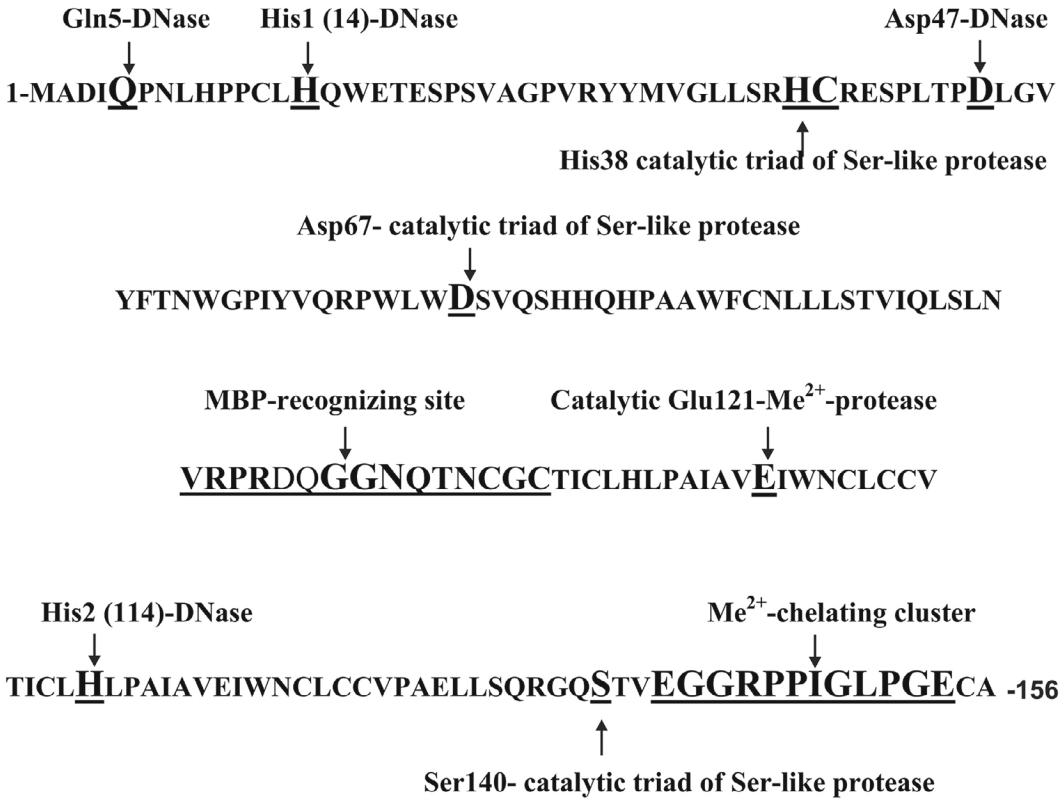

Fig. 1. Arrangement of amino acid residues in the catalytic triad (Asp–His–Ser) responsible for the serine protease-like activity, metal ion-chelating cluster, MBP recognition site, Glu-containing active site similar to that of Zn^{2+}-dependent metalloproteases, and active site responsible for the DNase activity of NGTA3-pro-DNase [136].

Taking this into account, analysis of enzymatic activity of NGTA3-pro-DNase yielded quite unexpected results [136]. Out of 25 recombinant MLCs, only NGTA3-pro-DNase cleaved both MBP and DNA. Incubation of NGTA3-pro-DNase with both PMSF (67%) and EDTA (36%) resulted in the inhibition of its protease activity. Metal ions activated proteolytic activity of NGTA3-pro-DNase in the following order: $Ca^{2+} \geq Ni^{2+} > Co^{2+} \approx Mn^{2+} \geq Cu^{2+} \approx Zn^{2+} \geq Mg^{2+}$, with $CaCl_2$ (3.0 mM) being the best activator. NGTA3-pro-DNase displayed two pH optima in MBP hydrolysis: after incubation with PMSF, the metalloprotease activity of this MLC reached the maximum at pH 8.6; in the presence of EDTA, the optimum of its serine protease-like activity was pH 7.0 [136]. NGTA3-pro-DNase treated with PMSF in the presence of 3.0 mM $CaCl_2$ (pH 7.0) displayed a higher affinity to MBP (K_M, 15.0 ± 1.1 μM) than in the presence of EDTA at pH 8.6 (K_M, 45 ± 1.1 μM). At the same time, the rate of MBP hydrolysis by the serine protease active site (k_{cat}, 0.40 ± 0.03 min^{-1}) was about twice as high compared to the metalloprotease active site (k_{cat}, 0.2 ± 0.04 min^{-1}) [136].

Magnesium ion (10 mM) has been shown to be the optimal cofactor for DNase I, while other metal ions activated this enzyme very weakly [120, 121]. The optimal concentrations of Mn^{2+}, Mg^{2+}, and Ni^{2+} for NGTA3-pro-DNase were lower (4-5 mM); the optimal concentration of Ca^{2+} and Zn^{2+} was 2 mM, and the optimal concentration of Co^{2+} and Cu^{2+} was 10 mM. The DNase activity of NGTA3-pro-DNase in the presence of metal ions decreased in the following order: $Mn^{2+} \approx Co^{2+} \geq Mg^{2+} > Cu^{2+} \approx Ni^{2+} \geq Ca^{2+} > Zn^{2+}$, which makes this MLC very different from canonical DNases. Under the optimal conditions, NGTA3-pro-DNase had the pH optimum at 6.5-6.6 and displayed a very high affinity to DNA [K_M = 2.0 ± 0.2 nM; $k_{cat} = (1.1 \pm 0.1) \times 10^{-3}$ min^{-1}] [136], which was approximately 3.5 orders of magnitude higher than DNase I (K_M, 46-58 μM) [124]. Therefore, NGTA3-pro-DNase is the first example of Abz with the active site combining three activities: serine protease-like, metalloprotease, and DNase [136].

How can we explain formation of NGTA3-pro-DNase active site with the three types of catalytic activities? As has been shown previously, MBP forms strong complexes with DNA in the blood [62, 63]. This can lead to the formation of new antigenic determinants (AGDs) at the junction between MBP and DNA molecules that would include fragments of both MBP and DNA sequences. In addition, MBP–DNA complexes can bind one or several metal ions. The process of V(D)J recombination can result

in the formation of unique variable domains specific against both DNA and MBP.

The homology between the protein sequences of NGTA1-Me-pro [133], NGTA2-Me-pro-Tr [134, 135], and NGTA3-pro-DNase [136] and sequences of known human serine proteases and Zn^{2+}- and Ca^{2+}-dependent proteases has been analyzed and fragments of these MLCs responsible for the specific binding of MBP and chelation of metal ions, as well as amino acid residues directly involved in catalysis, were identified. NGTA3-pro-DNase was found to contain sequences similar to the sequences of DNase I responsible for its DNase activity. The arrangement of amino acid residues responsible for the three activities of NGTA3-pro-DNase is shown in Fig. 1 [136].

Therefore, in contrast to classical enzymes, the active sites of Abzs can include structural elements of enzymes with different activities.

VARIATIONS IN THE PROPERTIES OF ABZYMES WITH THE CATALASE, PHOSPHATASE, AMYLASE, AND microRNase ACTIVITIES

Of particular interest is how changes in the BMSC differentiation profile during AID progression are related to the production of various Abzs at different stages of pathology development. C57BL/6 mice typically demonstrate a relatively slow spontaneous development of experimental autoimmune encephalomyelitis (EAE), which can be significantly accelerated by myelin oligodendrocyte glycoprotein (MOG) and DNA–histone complexes [58-63, 104-109, 111-112]. Spontaneous development of EAE in mice starts during the 3rd month of life.

Abzs with the amylase activity have been found in the cerebrospinal fluid and blood of MS patients [111] and in the blood of patients with AIDs [70] and autoimmune MRL-lpr/lpr mice [104, 105].

Abzs with the phosphatase activity were detected in the blood of rabbits immunized with DNA, RNA, DNase I, DNase II, and RNase A [137-139]. Abs hydrolyzing RNA and microRNAs were isolated from the blood of patients with AIDs [58-63, 79, 82, 83]. Abs with the oxidoreductase (including catalase) activity were isolated from human and animal blood [58-63, 97-103].

These data demonstrate that Abzs with the amylase, catalase, phosphatase, and microRNA-hydrolyzing activities can be formed as a result of immunization of humans and animals with specific autoantigens.

It was interesting to find out how the catalytic activities of Abzs can change at different stages of EAE in C57BL/6 mice starting from postnatal day 90.

The hydrolyzing activity of Abzs toward DNA, MBP, MOG, and histones demonstrated a relatively steady increase within 90-150 days after the start of the experiment [58-63, 118-125]. There was also a steady increase in the catalase, amylase, phosphatase, and microRNA-hydrolyzing activities of Abs in C57BL/6 mice beginning at the age of 3 months [140-143].

It should be noted that the catalytic properties of Abzs with different enzymatic activities varied significantly at different stages of spontaneous EAE, development, as well as during progression of EAE induced by MOG and DNA–histone complex. The profile of BMSC differentiation changed after appearance of B cells synthesizing Abzs with different pH optima and dependence (or lack of it) on metal ions. This could be seen most clearly for Abzs with the phosphatase activity. Figure 2 shows changes in the pH optimum of the phosphatase activity of IgGs during different stages in the development of spontaneous EAE

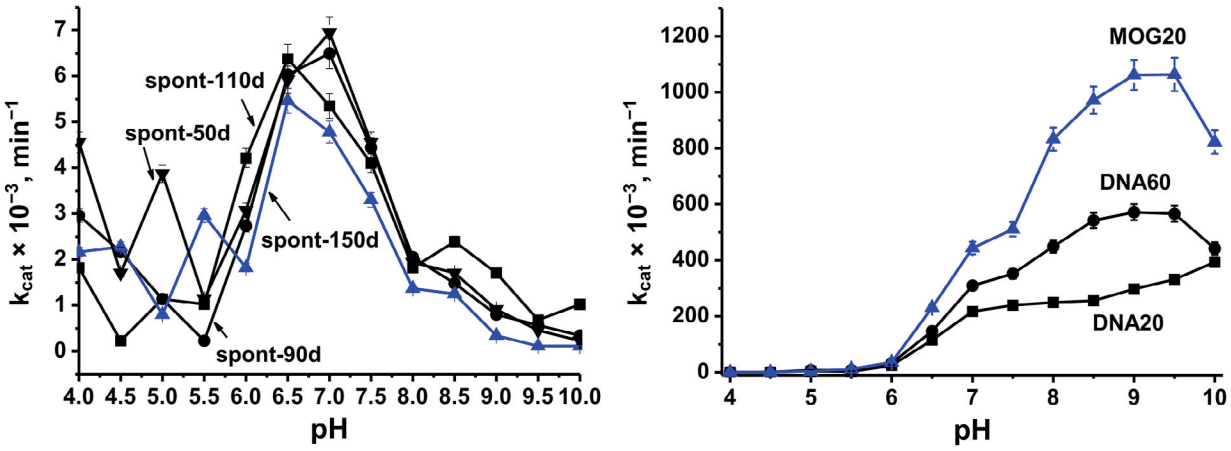

Fig. 2. pH dependence of the phosphatase activity (hydrolysis of *p*-nitrophenyl phosphate) of four Ab preparations corresponding to different periods of spontaneous EAE development: postnatal days 50 (Spont-50d), 90 (Spont-90d), 110 (Spont-110s), and 150 (Spont-150d) (a) and after immunization of 3-month-old mice with MOG (MOG20; 20 days) or DNA–histone complex: DNA20 (20 days) and DNA60 (60 days) (b) [143].

and after immunization of mice with MOG and DNA–histone complex.

During spontaneous development of EAE, the pH optimum for *p*-nitrophenyl phosphate hydrolysis by Abzs varied from 4 to 10. However, most IgG subfractions exhibited the maximal activity at pH 6.5-7.0 (Fig. 2a).

Immunization of mice with the DNA–histone complex and MOG resulted in the formation of Abzs the maximal phosphatase activity at pH 7.5 to 10.0 (with the peak activity at 8.5-9.5) (Fig. 2b). Similar to Abzs formed during spontaneous EAE development, these Abzs were able to hydrolyze *p*-nitrophenyl phosphate at pH 6.5-7.0, but their activity in this pH region was low and corresponded to the shoulders of pH dependence curves (Fig. 2b).

Canonical phosphatases are magnesium-dependent enzymes [144-146], The phosphatase activity of the obtained Abzs also depended on Mg^{2+} [143]. However, in contrast to Abzs formed during spontaneous EAE development, Abzs produced after immunization of mice with MOG and DNA–histone complex demonstrated a two-phase dependence on the Mg^{2+} concentration, which suggested the presence of different monoclonal Ab subfractions. Abs can significantly vary in the affinity for magnesium ions. Immunization with MOG led to a ~1060-fold increase in the phosphatase activity at pH 9.0 compared to Abs emerging during spontaneous EAE development. Immunization with the DNA–histone complex increased the phosphatase activity 570-fold (DNA60) and 310-fold (DNA20).

Similar changes in the pH optima and metal ion dependency were observed for the amylase, catalase, and microRNA-hydrolyzing activities of the formed Abzs. Immunization of mice with MOG and DNA–histone complex also resulted in the appearance of Abzs that hydrolyzed microRNAs at different sites.

Therefore, different stages of spontaneous and antigen-induced development of EAE can be accompanied by the activation of production of B cells secreting Abzs with different enzymatic properties. The most interesting and unexpected results were obtained for the cleavage of five histones and MBP by Abzs formed during spontaneous and antigen-induced development of EAE.

CHANGES IN THE SUBSTRATE SPECIFICITY OF ABZYMES WITH THE PROTEASE ACTIVITY AGAINST H1 HISTONE DURING PROGRESSION OF EAE

The most unexpected results demonstrating an extreme diversity and variation in the properties of Abzs at different stages of EAE progression were obtained in the studies of Abzs hydrolyzing five histones and MBP. As mentioned above, IgGs from the blood of HIV-infected patients against each of the five individual histones efficiently hydrolyzed all histones and MBP, and *vice versa*; anti-MBP Abs cleaved both MBP and each of the histones [131, 132]. These data demonstrated that Abzs against histones and MBP are characterized not only by the polyreactivity in the formation of complexes with the antigens [126-129], but also by the catalytic cross-reactivity, as discovered for the first time for Abzs from HIV-infected patients [89, 96, 132].

Analogous results were obtained in the detailed investigation of Abzs against five histones and MBP that were isolated from the serum of C57BL/6 mice at different stages of EAE development [147-150]. First, electrophoretically homogeneous and free from the admixtures of canonical proteases polyclonal IgGs against five individual histones and MBP were obtained from mice with EAE [147-150]. All procedures were performed with IgG preparations corresponding to different stages of spontaneous EAE development (designated as Spont) and those obtained after immunization of mice with MOG (designated as MOG) or DNA–histone complex (designated as DNA) (Table 1).

All obtained IgG preparations were assessed for the hydrolysis of H1, H2A, H2B, H3, and H4 histones. IgGs obtained against each individual histone hydrolyzed all five histones and MBP and, *vice versa*, the anti-MBP antibodies hydrolyzed MBP and each of the five histones [150-153]. IgG fractions with a high affinity to five individual histones and MBP were used to detect the corresponding cleavage sites in histones using matrix-activated laser desorption/ionization mass spectrometry (MALDI–MS) [147-150]. Although it is impossible to present the total data on the hydrolysis sites in this review, in order to understand what happens to the production of Abs against different histones at different stages of EAE development, it is necessary to describe the features of immune response in EAE mice using at least one histone as an example. Below, we present detailed analysis of H1 histone hydrolysis by Abs against all five histones and MBP.

First, we determined the sites cleaved in H1 histone by IgGs against 5 individual histones and MBP that were isolated at the start of the experiment from 3-month-old mice and then after spontaneous EAE development for 60 days (Fig. 3).

Immediately after addition of IgG antibodies, the preparation of H1 histone was almost homogeneous, demonstrating two signals corresponding to the single- (m/z 20719.1) and double-charged (m/z 10359.6) ions. The MALDI-MS spectra of the products of H1 histone hydrolysis were obtained for all 30 IgG preparations listed in Table 1 (8 to 10 spectra for each preparation; see Fig. 3 for the representative spectra).

Table 1. IgG preparations against individual histones (H1, H2A, H2B, H3, H4) and MBP corresponding to different stages of EAE progression [147-150]

Total IgG	no.	Preparation
Control (Cont); day 0 (start of the experiment); IgGs against 5 histones and MBP	1	Cont-aH1-0d
	2	Cont-aH2A-0d
	3	Cont-aH2B-0d
	4	Cont-aH3-0d
	5	Cont-aH4-0d
	6	Cont-MBP-0d
Spontaneous (Spont) EAE development, day 60; IgGs against 5 histones and MBP	7	Spont-aH1-60d
	8	Spont-aH2A-60d
	9	Spont-aH2B-60d
	10	Spont-aH3-60d
	11	Spont-aH4-60d
	12	Spont-aMBP-60d
Immunization with MOG; day 20; IgGs against 5 histones and MBP	13	MOG20-aH1
	14	MOG20-aH2A
	15	MOG20-aH2B
	16	MOG20-aH3
	17	MOG20-aH4
	18	MOG20-aMBP
Immunization with DNA–histone complex; day 20; IgGs against 5 histones and MBP	19	DNA20-aH1
	20	DNA20-aH2A
	21	DNA20-aH2B
	22	DNA20-aH3
	23	DNA20-aH4
	24	DNA20-aMBP
Immunization with DNA–histone complex; day 60; IgGs against 5 histones and MBP	25	DNA60-aH1
	26	DNA60-aH2A
	27	DNA60-aH2B
	28	DNA60-aH3
	29	DNA60-aH4
	30	DNA60-aMBP

The cleavage sites and relative efficiency of H1 histone hydrolysis by IgG preparations were established by averaging the data of 8-10 independent spectra [150] (see Fig. 4 for the data on H1 histone hydrolysis by the antibodies against H1, H2A, H2B, H3, and H4 histones formed after immunization of mice with MOG). All 30 IgG preparations hydrolyzed H1 histone at multiple sites that varied between different preparations.

To simplify the comparison of different sites in H1 histone cleaved by the Abs against different histones, we summarized them in the tables. As an example, Table 2 presents the data on the cleavage of H1 histone by IgG preparations against H1, H2A, and H2B histones at zero time and after 60 days of spontaneous EAE development (the tables for H1 histone cleavage by all 30 preparations were given in [150]).

The anti-H1 IgGs of 3-month mice (Cont-aH1-0d) hydrolyze this histone at 16 sites, while after the 60-day spontaneous development of EAE (Spont-aH1-60d) it is hydrolyzed at only 15 sites. For anti-H1 – abtibodies hydrolyzing H1 histone at 15 and 16 sites only 9 sites were different (Table 2).

During spontaneous development of EAE for 60-day, the number of sites in H1 histone cleaved by IgGs against H2A histone increased from 15 (Cont-aH2A-0d) to 25 (Spont-aH2A-60d), including 11 new major and medium sites (Table 2). The number of sites hydrolyzed by Cont-aH2B-0d was only 4 and then increased to 8 by day 60 of the experiment (Spont-aH2B-60d).

The pattern was slightly different in the case of H1 histone hydrolysis by IgGs against H3 and H4 histones. The number of cleavage sites for Spont-aH3-60d decreased to 10 from 17 (Cont-aH3-0d), and only one site was common for both IgG preparations (Table 2).

The maximum number of cleavage sites (23) at zero time was found for Cont-aH4-0d, but this number decreased to 17 by day 60 of spontaneous EAE development (Spont-aH4-60d). Both IgG preparations cleaved 5 major sites each, and these sites did not overlap (Table 2).

Immunization of mice with MOG led to a very dramatic change in the BMSC differentiation profile compared to profiles at zero time and after spontaneous EAE development [106-109, 147-150], including appearance of B lymphocytes secreting anti-H1 histone antibodies with different properties. Immunization with MOG increased the number of sites cleaved by anti-H1 IgGs from 16 (Cont-aH1-0d) to 26 [150]: 4 major and several minor new sites were found for MOG20-aH1. Only 5 out of 26 sites hydrolyzed by MOG20-aH1 were the same as 5 out of 15 sites cleaved by Abs formed by day 60 of spontaneous EAE development (Spont-aH1-60d).

Interestingly, immunization of mice with MOG led to a significant decrease in the number of

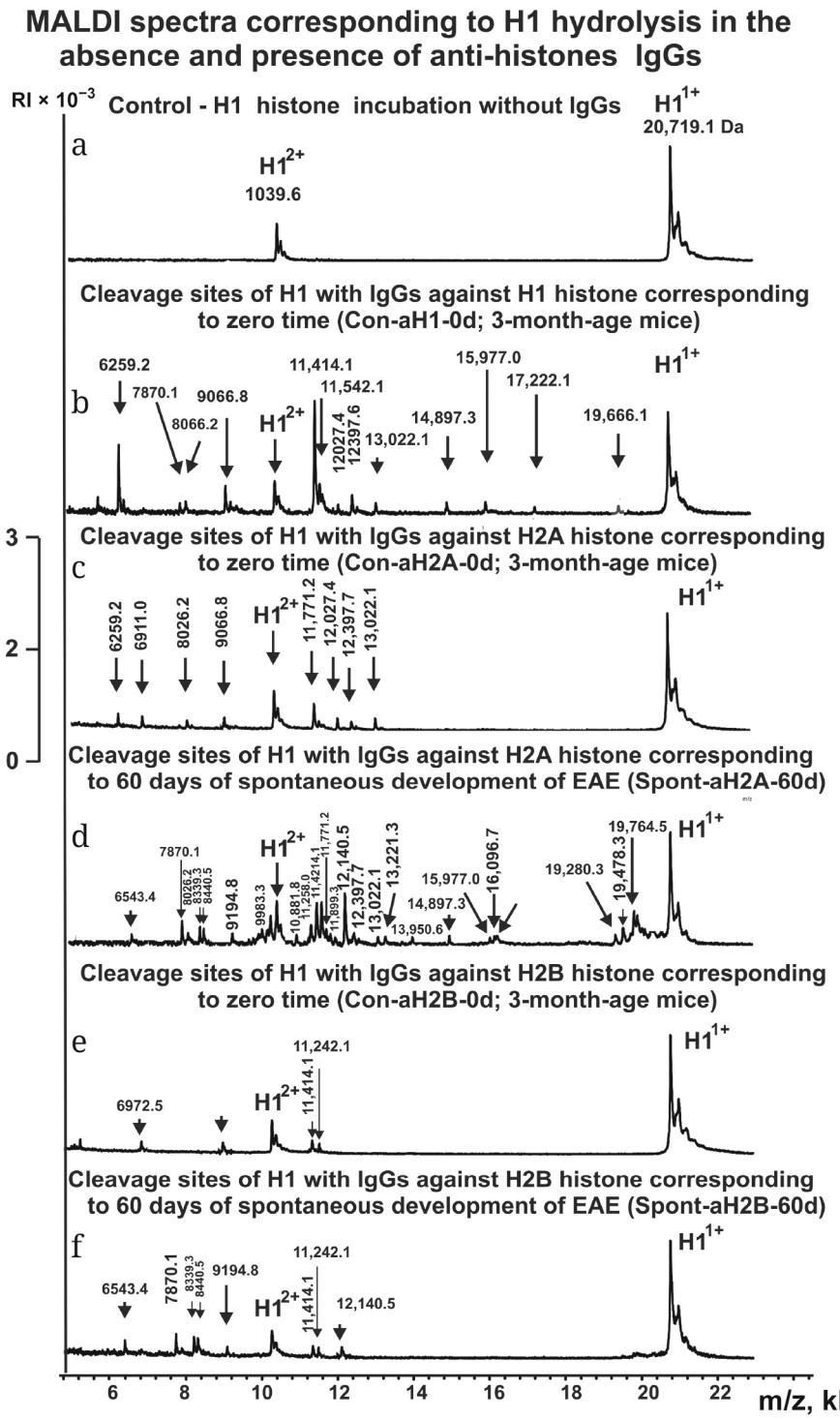

Fig. 3. MALDI-MS spectra of products of H1 histone hydrolysis in the absence (a) and presence of anti-histone IgGs: Cont-aH1-0d (b), Cont-aH2A-0d (c), Spont-aH2A-60d (d), Cont-aH2B-0d (e), and Spont-aH2B-60d (f). All designations of IgGs and mass/charge ratio (*m*/*z*) values are from [150].

hydrolyzed sites from 15 (Cont-aH2A-0d) to 4 (MOG20-aH2A). These Abzs shared only one common major cleavage site (F106-K107). One minor site hydrolyzed by MOG20-aH2A was the same as one medium site cleaved by Spont-aH1-60d.

The number of sites hydrolyzed MOG20-aH2B increased to 5 from 4 (Cont-aH2B-0d). All four sites cleaved by Cont-aH2B-0d were minor, and four out of 5 sites cleaved by MOG20-aH2B were major.

Immunization with MOG decreased the number of hydrolyzed sites from 17 (Cont-aH2B-0d) to 7 (MOG20-aH3). Only one minor hydrolysis site (R93-L94) was common for these two IgG preparations. MOG20-aH3 and Spont-aH3-60d shared two common sites.

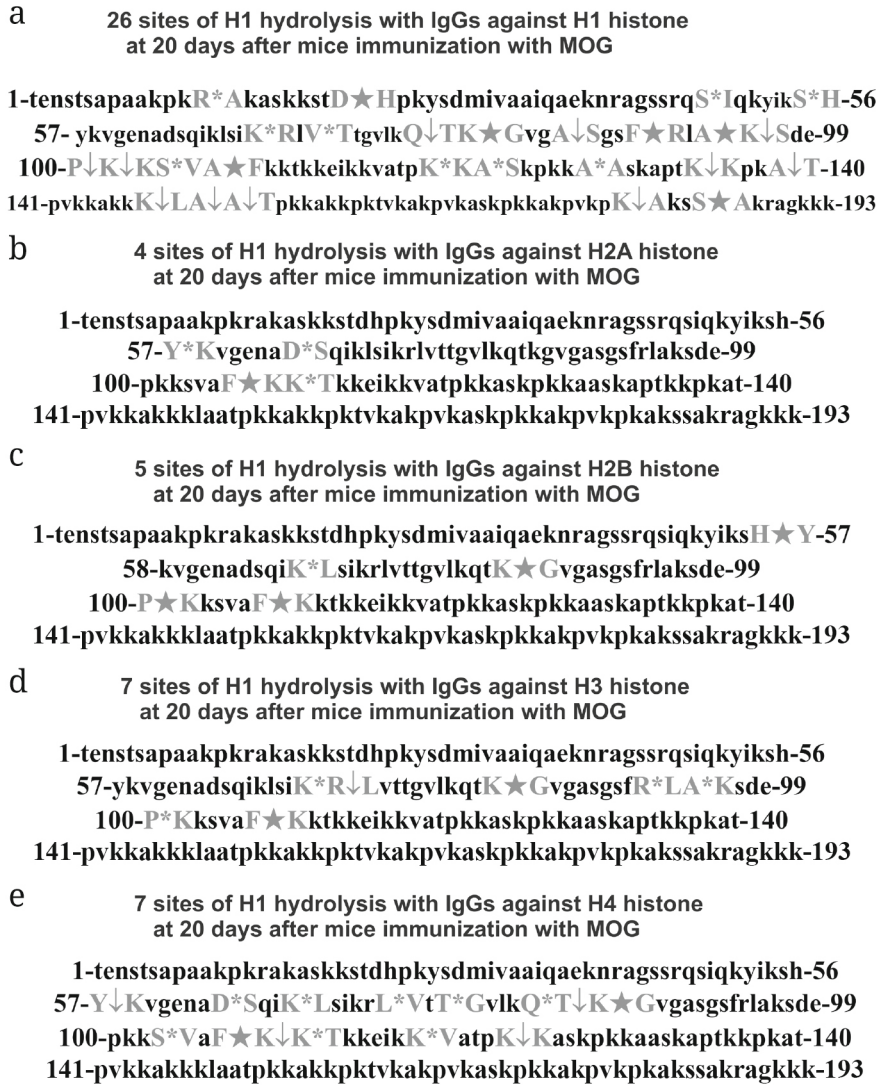

Fig. 4. Cleavage sites in H1 histone hydrolyzed by IgGs against five histones formed by day 20 after immunization of mice with MOG: MOG20-aH1 (a), MOG20-aH2A (b), MOG20-aH2B (c), MOG20-aH3 (d), and MOG20-aH4 (e). Major, medium, and minor cleavage sites are indicated with stars (★), arrows (↓), and asterisks (*), respectively [150].

The number of sites hydrolyzed by MOG20-aH4 decreased to 17 from 24 (Cont-aH4-0d). Only three sites were the same for the two preparations, but they were hydrolyzed with different efficiency.

In general, immunization of mice with MOG led to a dramatic increase in the number of sites only for the IgGs against H1 histone. For all other Abzs, with the exception of anti-H2B histone IgGs, the number of cleavage sites decreased. However, in all the cases, the cleavage sites in H1 histone at zero time and after 60 days of spontaneous EAE development were significantly different from those identified after immunization with MOG [150].

The development of EAE in mice can also be accelerated by immunization with the DNA–histone complex [146], although the profile of BMSC differentiation in this case differed from the profiles observed during spontaneous EAE development and after immunization with MOG. As a result, Abzs against individual histones hydrolyzed H1 histone at different sites compared to Abzs formed during spontaneous EAE development and after immunization with MOG.

Twenty days after immunization of mice with the DNA–histone complex, the number of sites in H1 histone hydrolyzed by DNA20-aH1 was the same (16) as at zero time (Cont-aH1-0d), unlike during spontaneous EAE development. However, only 7 out of 16 sites were identical for the two Abz preparations. The number of sites hydrolyzed 20 days after immunization with MOG (MOG20-aH1) was 26 [150], and only 4 sites were identical for MOG20-aH1 and DNA20-aH1.

Table 2. Cleavage sites in H1 histone hydrolyzed by IgGs against H1, H2A, and H2B histones at zero time and after 60 days of spontaneous EAE development (from [150])

Number and type of sites									
Cont-aH1-0d	Spont-aH1-60d	Cont-aH2A-0d	Spont-aH2A-60d	Cont-aH2B-0d	Spont-aH2B-60d	Cont-aH3-0d	Spont-aH3-60d	Cont-aH4-0d	Spont-aH4-60d
16	15	15	25	4	8	17	10	23	17
*K11-P12**	–	–	–	–	–	–	–	–	–
–	–	–	**R14-A15***	–	–	–	–	–	*R14-A15*
–	–	–	–	–	–	–	–	**D23-H24**	**D23-H24***
A33-A36	–	–	–	–	–	–	–	–	–
F33-A34	–	–	–	–	–	–	–	–	–
–	–	–	*S44-S45*	–	–	–	–	–	–
–	–	–	–	–	–	–	**Y52-I53**	–	–
–	–	–	–	–	–	–	–	*S55-H56*	*S55-H56*
Y57-K58	**Y57-K58**	–	–	–	–	–	**Y57-K58**	–	–
–	–	–	–	–	–	*V59-G60*	–	**V59-G60**	**V59-G60**
–	–	-	**G60-E61**	–	**G60-E61**	**G60-E61**	–	–	–
–	–	*N62-A63*	*N62-A63*	–	–	–	–	–	–
–	–	–	–	*D64-S65*	–	–	–	–	–
–	–	–	–	–	–	**I67-K68**	–	**I67-K68**	–
–	–	–	–	–	**K68-L69**	–	–	–	–
–	–	–	–	–	–	–	–	**I71-K72**	**I71-K72**
–	–	–	**K72-R73**	–	–	–	R73-L74	–	–
R73-L74	*R73-L74*	*R73-L74*	*R73-L74*	–	–	–	–	–	–
–	–	–	–	–	–	–	–	**L74-V75**	**L74-V75**
–	–	–	–	–	–	*V75-T76*	–	*V75-T76*	*V75-T76*
T76-T77	**T76-T77**	–	–	–	–	–	–	–	–

Table 2 (*cont.*)

Number and type of sites									
Cont-aH1-0d	Spont-aH1-60d	Cont-aH2A-0d	Spont-aH2A-60d	Cont-aH2B-0d	Spont-aH2B-60d	Cont-aH3-0d	Spont-aH3-60d	Cont-aH4-0d	Spont-aH4-60d
–	–	–	**T77-G78**	–	**T77-G78**	–	–	–	–
–	–	–	**V79-L80**	–	*V79-L80*	–	–	–	–
L80-K81	**L80-K81**	**L80-K81**	–	–	–	–	–	–	–
–	–	–	*K81-Q82*	–	–	–	–	–	–
–	*Q82-T83*	*Q82-T83*	*Q82-T83*	–	–	*Q82-T83*	-	*Q82-T83*	*Q82-T83*
T83-K84	*T83-K84*	–	–	–	–	–	–	–	–
K84-G85	*K84-G85*	**K84-G85**	**K84-G85**	*K84-G85*	*K84-G85*	–	–	–	–
–	–	–	–	–	–	**G85-V86**	–	–	–
V86-G87	–	–	–	–	–	–	–	–	–
–	–	–	**A88-S89**	–	–	–	**A88-S89**	–	–
–	**F92-R93**	–	–	–	–	–	–	–	–
–	–	–	–	–	–	*R93-L94*	–	*R93-L94*	-
–	**L94-A95**	–	–	–	–	–	–	–	–
–	–	–	**D98-E99**	–	–	**D98-E99**	–	**D98-E99**	–
–	–	–	–	–	–	–	–	*E99-P100*	–
–	–	–	*K101-K102*	–	–	*K101-K102*	–	**K101-K102**	–
–	–	–	K102-S103	–	–		–	–	–
–	–	–	–	–	–	**S103-V104**	–	**S103-V104**	**S103-V104**
–	–	–	–	–	–	**V104-A105**	–		*V104-A105*
–	**A105-F106**	–	–	–	–	**A105-F106**	–	**A105-F106**	**A105-F106**
F106-K107	**F106-K107**	**F106-K107**	–	*F106-K107*	*F106-K107*	–	**F106-K107**	–	–
K107-K108	**K107-K108**	–	**K107-K108**	–	K107-K108	–	**K107-K108**	–	–

Table 2 (*cont.*)

Number and type of sites									
Cont-aH1-0d	Spont-aH1-60d	Cont-aH2A-0d	Spont-aH2A-60d	Cont-aH2B-0d	Spont-aH2B-60d	Cont-aH3-0d	Spont-aH3-60d	Cont-aH4-0d	Spont-aH4-60d
K108-T109	*K108-T109*	*K108-T109*	–	*K108-T109*	–	–	**K108-T109**	–	–
–	–	–	–	–	–	–	–	**K110-K111**	–
–	–	–	–	–	–	**E112-I113**	*E112-I113*	**E112-I113**	–
–	–	–	–	–	–	–	–	–	**I113-K114**
–	–	**K114-K115**	*K114-K115*	–	**K114-K115**	–	–	–	–
–	–	–	–	–	–	*K115-V116*	–	–	–
K120-K121	*K120-K121*	*K120-K121*	*K120-K121*	–	–	–	–	*K120-K121*	–
–	–	–	*A122-S123*	–	–	–	*S123-K124*	–	–
–	–	–	–	–	–	–	-	*K126-K127*	*K126-K127*
–	–	–	–	–	–	*A128-A129*	-	*A128-A129*	*A128-A129*
–	–	–	*K131-A132*	–	–	–	–	–	–
K138-A139	*K138-A139*	-	*K138-A139*	–	–	–	–	–	–
–	–	–	–	–	–	**A139-T140**		**A139-T140**	**A139-T140**
–	–	–	–	–	–	*K147-K148*	–	–	–
K148-L149	–	–	*K148-L149*	–	–	–	–	–	–
–	–	–	A150-A151	–	–	–	–	*A150-A151*	**A150-A151**
–	–	–	-	–	–	–	*A151-T152*	*A151-T152*	–
–	–	–	**K170-A171**	–	–	–	–	–	–
–	–	–	–	–	–	–	–	*K181-A182*	*K181-A182*
–	–	–	**S184-S185**	–	–	–	–	–	–

Note. * Molecular weights of H1 histone cleavage products and cleavage sites were determined based on the data from 8 to 10 spectra. ** Major, medium, and minor sites are shown in bold, standard, and underlined italic fonts, respectively. The absence of histone cleavage at a particular site is indicated with a dash (–).

MOG20-aH1 efficiently cleaved H1 histone at the C-terminus (K120-A186), while no cleavage sites for DNA20-aH1 were identified in this region. The number of sites hydrolyzed by DNA20-aH2A decreased from to 13 to 15, and only one major cleavage site (F106-K107) was common for Cont-aH2A-0d and DNA20-aH2A.

Immunization of mice with MOG decreased the number of sites cleaved by anti-H2A Abzs from 15 to 4, and only one (Y57-K58) out of these four cleavage sites was hydrolyzed by DNA20-aH2A [150].

The number of sites hydrolyzed by DNA20-aH2B increased from to 5 from 4 compared to zero time (Cont-aH2B-0d); 4 of these sites were common for both preparations. However, only 2 sites were common for DNA20-aH2B and MOG20-aH2B. Therefore, immunization of mice with the DNA–histone complex led to a decrease in the number of anti-H2B IgG preparations capable of hydrolyzing H1 histone.

Twenty days after immunization with the DNA–histone complex, the number of sites hydrolyzed by anti-H3 IgGs decreased from 17 to 9. Interestingly, all sites cleaved by DNA20-aH3 were completely different from the sites identified at zero time (Cont-aH3-0d). After immunization of mice with MOG, the number of sites decreased to 7 (MOG20-aH3) from 17, and 3 out of these 7 sites were the same as for DNA20-aH3.

The maximal number of cleavage sites in H1 histone (23) at zero time was found for the anti-H4 antibodies (Cont0aH4-0d); however, it decreased to 10 after immunization with the DNA–histone complex (DNA20-aH4) and to 17 after immunization with MOG (MOG20-aH4). Out of 10 sites found for DNA20-aH4, 7 were identical to those for MOG20-aH4 and only two sites were shared with Cont-aH4-0d.

BMSC differentiation profile could change several times during spontaneous EAE development and after immunization with MOG or DNA–histone complex. In the case of immunization with MOG, there were only three well-pronounced stages: the onset of accelerated EAE development (7-8 days after immunization), acute phase (days 20-21) characterized by the maximum activity of Abzs, and remission (after ~30 days) accompanied by a slow decrease in the Abz activity. The same three stages were observed after immunization with the DNA–histone complex; however, they were followed by another acute phase after ~50-60 days that was characterized by a dramatic increase in the activity of Abzs, especially those with the DNase activity [107]. In view of the above, we analyzed the activity of Abzs 60 days after immunization with the DNA–histone complex.

Interestingly, compared to the spontaneous EAE development, immunization of mice with the DNA–histone complex led to the increase in the number of cleaved sites in H1 histone by DNA60-aH2B and DNA60-aH3 60 days after immunization. However, the number of sites hydrolyzed by IgGs against the other three histones (H1, H2A, and H4) decreased.

Among 8 sites hydrolyzed by DNA60-aH1, only 3 were shared with Spont-aH1-60d [150], and none were identical to 16 cleavage sites observed for Cont-aH1-0d. In contrast to the immunization with the DNA–histone complex, immunization with MOG increased the number of cleaved sites from 16 (Cont-aH1-0d) to 26 (MOG20-aH1), i.e., the difference in the number sites cleaved by MOG20-aH1 and DNA60-aH1 was 18.

Spontaneous EAE development for 60 days resulted in the production of Abs that hydrolyzed H1 histone at 25 sites (Spont-aH2A-60d), whereas immunization with the DNA–histone complex decreased the number of sites to 15 (DNA60-aH2A), and only 3 sites were shared by both Abz preparations. The number of sites hydrolyzed by Cont-aH2A-0d and DNA60-aH2A was comparable (16 and 15, respectively), but only 1 weak site was common for these preparations. Among the 4 cleavage sites found for MOG20-aH2A, 2 sites where the same as 2 sites (out of 8) hydrolyzed by Spont-aH2A-60d.

Spont-aH2B-60d and DNA60-aH2B hydrolyzed H1 histone at 8 and 12 sites, respectively. Cont-aH2B-0d cleaved H1 histone at only 4 sites; 2 of them were shared with DNA60-aH2B. Out of the 5 sites cleaved by MOG20-aH2B, 3 sites were common with DNA60-aH2B.

Spontaneous development of EAE decreased the number of sites hydrolyzed by anti-H3 histone Abs from 17 (Cont-aH3-0d) to 10 (Spont-aH3-60d), whereas DNA60-aH2B cleaved H1 histone at 16 sites. Spont-aH3-60d and DNA60-aH2B shared only 3 cleavage sites. Among the 7 sites hydrolyzed by MOG20-aH3, 4 were common with Spont-aH3-60d (16 cleavage sites).

Spont-aH4-60d hydrolyzed H1 histone at 17 sites, while DNA60-aH4 cleaved it only at 6 sites. Moreover, in the latter case, formed B lymphocytes produced different types of Abs, as none of these 6 sites were identical to the sites identified for Spont-aH4-60d, and only 4 sites were shared with Cont-aH4-0d. Five sites were common with MOG20-aH4 (17 sites), and 5 sites were shared with DNA60-aH4 (6 sites).

The data on changes in the number of cleavage sites in H1 histone at different stages of spontaneous EAE development (Table 3) are of particular interest. Depending on the specificity of antibodies (anti-H1, H2A, H2B, H3, or H4), the number of cleavage sites after 60 days of spontaneous EAE development either remained almost unchanged, increased, or decreased: H1 (16→15), H2A (15→25), H2B (4→8), H3 (17→10), and H4 (23→17). Immunization of mice with the DNA–histone complex led the increase in the number of sites cleaved by the anti-H3 histone Abs from 9 (DNA20-aH3) to 16 (DNA60-aH3). during the period from day 20 to day 60. Significant changes in the number and type of hydrolyzed sites were observed for the Abs

Table 3. Changes in the number of cleavage sites in five individual histones hydrolyzed by Abs against these histones and MBP at different stages of EAE development

Antibody preparation*									
Cont-aH1-0d	Spont-aH1-60d	Cont-aH2A-0d	Spont-aH2A-60d	Cont-aH2B-0d	Spont-aH2B-60d	Cont-aH3-0d	Spont-aH3-60d	Cont-aH4-0d	Spont-aH4-60d
Number of cleavage sites in H1 histone									
16	15	15	25	4	8	17	10	23	17
Number of cleavage sites in H2A histone									
7	28	4	17	8	27	15	12	8	7
Number of cleavage sites in H2B histone									
4	28	9	6	6	10	6	15	6	7
Number of cleavage sites in H3 histone									
15	21	16	11	13	13	11	12	18	6
Preparations of antibodies after immunization with the DNA–histone complex									
DNA20-aH1	DNA20-aH2A	DNA20-aH2B	DNA20-aH3	DNA20-aH4	DNA60-aH1	DNA60-aH2A	DNA60-aH2B	DNA60-aH3	DNA60-aH4
Number of cleavage sites in H1 histone									
16	13	5	9	10	8	16	12	16	6
Number of cleavage sites in H2A histone									
11	27	19	11	23	11	22	35	23	24
Number of cleavage sites in H2B histone									
7	8	10	5	15	33	3	11	10	6
Number of cleavage sites in H3 histone									
20	12	6	9	8	7	9	7	13	5

Note. * Abs preparations are described in Table 1 [147-150].

against other histones during the same time period of time: anti-H1 (16→8), anti-H2A (13→16), anti-H2B (5→12), and anti-H4 (10→6). In the case of spontaneous EAE development, there was only a weak overlap of cleavage sites on days 20 and 60. Therefore, both spontaneous and antigen-induced development of EAE was accompanied by changes in the BMSC differentiation profile that resulted in the production of new lymphocytes secreting Abzs that hydrolyzed H1 histone at different number of sites and different types of sites.

Data on the sites of histones hydrolysis after immunization of mice with MOG or DNA–histone complex are presented in Table 4.

As mentioned above, Abs against all five histones hydrolyzed not only all individual histones, but also MBP, and, *vice versa*, anti-MBP Abs efficiently hydrolyzed all five histones.

Anti-MBP antibodies at zero time (Cont-aMBP) hydrolyzed H1 histone only at 5 sites; 20 days after immunization with MOG and DNA–histone complex, the number of cleavage sites decreased to 3 and 2, respectively; 60 days after the immunization with the DNA–histone complex, the number of sites increased to 8 (DNA60-aMBP) (Table 4) Therefore, the number of sites in H1 histone hydrolyzed by anti-MBP Abs was less than for the Abs against five individual histones. In addition, only few sites of hydrolyzed

Table 4. Changes in the number of cleavage sites in five individual histones hydrolyzed by Abs against these histones and MBP after immunization of mice with MOG or DNA-histones complex

Preparations of antibodies after immunization of mice with MOG and \DNA–histones complex*								
MOG20-aH1	MOG20-aH2A	MOG20-aH2B	MOG20-aH3	MOG20-aH4	Cont-aMBP	MOG20-aMBP	DNA20-aMBP	DNA60-aMBP
Number of cleavage sites in H1 histone								
26	4	5	7	17	5	3	2	8
Number of cleavage sites in H2A histone								
15	11	7	6	11	19	21	22	18
Number of cleavage sites in H2B histone								
26	26	7	6	11	11	14	9	4
Number of cleavage sites in H3 histone								
15	12	16	8	20	14	12	9	8

Note. * Abs preparations are described in Table 1 [147-150].

by anti-MBP Abzs coincided with the sites cleaved by anti-histone Abs [150].

The above detailed analysis of H1 histone hydrolysis by Abs against all five histones and MBP formed at different stages of EAE development was performed to demonstrate very complex changes in the BMSC differentiation profile resulting in the formation of B lymphocytes producing Abs with very different properties.

CHANGES IN THE SUBSTRATE SPECIFICITY OF ABZYMES AGAINST H2A, H2B, H3, AND H4 HISTONES

Similar detailed analysis was performed for the hydrolysis of other histones (H2A, H2B, H3, and H4) by Abs against all five histones and MBP (see [147-150]). As can be seen from Tables 3 and 4, all Ab preparations hydrolyzed histones at different number of sites.

The minimal number of cleavage sites (2 and 3) was found for H1 histone hydrolysis by DNA20-aMBP and MOG20-aMBP. Three antibody preparations hydrolyzed different histones at 4 sites, and two of them at 5 sites (Table 4). The maximal number of cleavage sites was found for DNA60-aH2B and DNA60-aH1 in the hydrolysis of H2A (35 sites) and H2B (33 sites) histones, respectively.

Anti-H1 Abs at zero time (Cont-aH2A-0d) hydrolyzed H2A histone at 7 sites. After 60 days of spontaneous EAE development, the number of cleaved sites increased to 28 (Spont-aH2A-60d), and only 5 of them were common for the two preparations [148]. The number of sites in H2A histone hydrolyzed by anti-H2B antibodies at zero time (Cont-aH2B-0d) was 8, but increased to 27 after 60 days of spontaneous EAE development (Spont-aH2B-60d). Each of these preparations had 4 major cleavage sites that did not overlap. The number of sites cleaved by Spont-aH3-60d preparation decreased to 12 from 15 (Cont-aH3-0d), and no identical sites have been identified for these two preparations. After 60 days of spontaneous EAE development, the number of cleavage sites in H2A histone anti-H4 histone Abs decreased from 8 (Cont-aH4-0d) to 7 (Spont-aH4-60d), and all hydrolysis sites turned out to be different. Similar changes in the number and type of sites hydrolyzed in H2A histone was found for all preparations obtained after spontaneous development of EAE and immunization of mice with MOG and DNA–histone complex [148], as well as for hydrolysis of all five histones by Abs against each of the five histones [147-150].

Number of sites for antibodies against H1 histone in H2B hydrolysis corresponding to 60 days after immunization of mice with DNA–histone complex is 29. Eleven out of 29 antibody preparations hydrolyzed different histones at 23-28 sites (Table 3). These data demonstrate that EAE development, either spontaneous or induced by MOG and DNA–histone complex, was accompanied by specific changes in the BMSC differentiation profiles, resulting in the appearance of B lymphocytes that synthesized antibodies with highly different properties. These changes led not only to the production of antibodies hydrolyzing five histones

at different number of sites, but also cleaving different sites and with different efficiency.

The obtained data provide a lot of examples for changes in the cleavage sites in histones, even when the number of sites did not change dramatically (see above for H1 histone hydrolysis by different antibodies).

The number of sites in H2A histone hydrolyzed by anti-H2B antibodies at zero time (Cont-aH2B-0d) was 8, but increased to 27 after 60 days of spontaneous EAE development (Spont-aH2B-60d). Each of these preparations had 4 major cleavage sites that did not overlap. The number of sites cleaved by Spont-aH3-60d preparation decreased to 12 from 15 (Cont-aH3-0d), and no identical sites have been identified for these two preparations. After 60 days of spontaneous EAE development, the number of cleavage sites in H2A histone anti-H4 histone Abs decreased from 8 (Cont-aH4-0d) to 7 (Spont-aH4-60d), and all hydrolysis sites turned out to be different. Similar changes in the number and type of sites hydrolyzed in H2A histone was found for all preparations obtained after spontaneous development of EAE and immunization of mice with MOG and DNA–histone complex [148], as well as for hydrolysis of all five histones by Abs against each of the five histones [147-150].

During spontaneous development of EAE, the number of sites in H2B histone hydrolyzed by anti-H2A antibodies decreases from 9 (Cont-aH2A-0d) to 4 (Spont-aH2A-60d); only two sites were identical [149]. The number of sites cleaved by Cont-aH2B-0d was only 6, but increases to 10 by day 60 of spontaneous EAE development of (Spont-aH2B-60d); again, only 2 sites were common for the both preparations. The number of sites hydrolyzed by Abs against H4 histone increased from 6 (Cont-aH4-0d) to 7 (Spont-aH4-60d); however, all sites, except for one, were different.

Spontaneous EAE development led to the increase in the number of sites in H3 histone hydrolyzed by anti-H1 histone IgGs from 15 (Cont-aH1-0d) to 21 (Spont-aH1-60d), with the formation of 9 major and medium sites. Immunization of mice with MOG had no effect on the number of hydrolysis sites compared to zero time, but only 7 out of 15 sites for Cont-aH1-0d and MOG20-aH1 were identical. The number of sites in H3 histone cleaved by anti-H2A histone IgGs was maximal (16) at zero time (Cont-aH2A-0d), but then decreases to: 11 (Spont-aH2A-60d), 12 (MOG20-aH2A and DNA20-aH2A), and 10 sites (DNA60-aH2A). Interestingly, there was not a single common site for all five of the anti-H2A histone Ab preparations. The development of EAE from day 20 to 60 after immunization with the DNA–histone complex occurred in such a way that DNA20-aH2A and DNA60-aH2A shared only two cleavage sites in H3 histone. An interesting feature of anti-H2A Abs was that the sites recognized by Cont-aH2A-0d and Spont-aH2A-60d were identified vary rarely for the other Ab preparations.

When analyzing such data, it is necessary to take into account that changes in the BMSC differentiation profile results in the synthesis of antibodies by B cells in the cerebrospinal fluid [111-113]. Abs isolated from the cerebrospinal fluid from MS patients were 30-60-fold more active in the hydrolysis of DNA, MBP, and oligosaccharides than Abs isolated from the sera of the same patients [111-113]. In addition, different stages of spontaneous development of SLE and EAE were accompanied by several changes in the in the BMSC differentiation profile [104-109].

Analysis of catalytic activity of Abs has shown for the first time that autoAbs, 30-40% of which are Abzs, can be very different in their properties even at the early stages of AID development. In view of the above, the question about the causes of exceptional diversity of Abs and Abzs in patients with autoimmune and neurological diseases is of particular interest.

DISCUSSION

There are still many questions about immune response to various antigens in autoimmune, neurological, and some viral diseases. Theoretically, human immune system is capable of synthesizing about a million Abs with very different properties against the same antigen [118]. Yet, it remains unclear how many types of Abs and with what properties can be formed in healthy people and patients with autoimmune, neurological, and viral diseases. Unfortunately, these questions cannot be answered using such common techniques as EIA or affinity chromatography of Abs on specific sorbents, as the possibilities of these methods in the analysis of diversity of Abs formed in response to exogenous and endogenous antigens and of the role of these Abs in the pathogenesis of various diseases are very limited [58-63]. To estimate a probable number of Abs in the blood of SLE patients, researchers analyzed monoclonal Abs obtained by the phage display technique [122, 123, 133-136]. It was found that the number of anti-DNA and anti-MBP Abs in the blood of SLE patients can be over 3-4 thousands, and approximately 30-40% of them are Abzs capable of hydrolyzing DNA and MBP. However, this approach also cannot provide full understanding of the diversity of produced antibodies.

One of the methods for a more detailed analysis of the properties of Abs is evaluation of their catalytic activity in the hydrolysis of various exo- and endogenous antigens. Catalytic Abs can play either positive or negative role in disease development. For example, HIV-infected patients produce Abs against viral reverse transcriptase and integrase that can cleave

these two proteins, thus slowing down the development of the acquired immunodeficiency syndrome [58-63, 131]. Other Abs play a negative role in the pathogenesis of viral, autoimmune, and neurological diseases. For example, Abs capable of hydrolyzing DNA and histones can penetrate through the cellular and nuclear membranes, cleave DNA and histones in chromatin, and stimulate cell apoptosis [34, 58-63, 75], which "fuels" autoimmunity in many pathological states. The cleavage of MBP in the myelin sheath of neurons by anti-MBP antibodies can lead to the development of MS [58-63]. The fact that Abzs against five histones hydrolyzed each of these histones and MBP, while Abs against MBP hydrolyzed MBP and all five histones, deserves special attention [62, 63, 89, 106-109, 147-149] and can be used for a more detailed analysis of potential role of Abzs against different antigens in the pathogenesis of AIDs.

As mentioned above, the autoimmune processes in patients with AIDs and some neurological and viral diseases are associated with changes in the BMSC differentiation profile and expansion of autoreactive B cell clones [62, 63, 89, 106-109, 147-149]. However, during spontaneous development of EAE in mice, such changes occurred in several stages. Moreover, the BMSC differentiation profile in the case of accelerated EAE development triggered by immunization with MOG or DNA–histone complex was absolutely different compared to profile characteristic of spontaneous EAE development [26-28, 140-143]. So, the important question is how changes in the BMSC differentiation profile influence production of B cells synthesizing autoAbs and Abzs harmful for humans and animals. Some studies have shown that the ratio between catalytically active and inactive autoAbs varies dramatically at the early stages of EAE development in mice [26-28, 140-143]. However, Abzs catalyzing reactions corresponding to different EAE stages can vary greatly in their activity, pH optimum, dependence (or lack of it) on mono- and divalent metal ions, affinity to antigens (substrates), isoelectric point, thermostability, etc. [58-63, 106-109, 147-150]. The most pronounced changes in the BMSC differentiation profile at different EAE stages were found for hydrolysis of histones and MBP [147-150]. As shown above, the cleavage patterns for H1, H2A, H2B, H3, and H4 histones observed for Abs against these histones at different stages of EAE development accelerated by immunization with MOG or DNA–histone complex significantly differed in the number and types of hydrolyzed sites. For example, the number of cleavage sites in H1 histone varied from 2 to 26 depending on the IgG preparation [150]. The same was observed for hydrolysis of other four histones [147-150]. However, even if when the number of cleaved sites was significant, the overlapping of these sites for any pair out of 30 Ab preparations was minimal. These data have posed a series of new questions on the possibility of formation of Abs and Abzs with absolutely different properties at different stages of spontaneous EAE development and after immunization with MOG and DNA–histone complex. This could be due to several factors.

First, human MS is an autoimmune pathology whose development includes at least two or even three stages [151]. The cascade of reactions at the first stage of inflammation is very complex and involves chemokines, cytokines, proteins, enzymes, macrophages, and cells producing the NO radical [151]. The coordinated action of B and T cells, inflammation mediators, complement system, and autoAbs results in the formation of demyelination foci and impaired axonal conduction. The following neurodegenerative stage of the disease is directly associated with the destruction of nervous tissue [151]. Therefore, medical, immunological, and biochemical indicators of MS should be analyzed with regard to the features of each particular disease stage, including changes in systemic metabolism, immunoregulation, and depletion of adaptive and compensatory mechanisms [151].

It is believed that the development of AIDs, including MS, can be stimulated by foreign (bacterial or viral) antigens [152-156]. Molecular mimicry associated with the homology between the molecules of human body, bacteria, and viruses (e.g., Epstein–Barr, measles, hepatitis B, herpes simplex, and influenza viruses, papillomaviruses) can trigger autoimmune processes in MS and other AIDs [58-63, 152-156]. Some viral and bacterial antigens are able to penetrate through the blood–brain barrier and stimulate specific changes in the bone marrow, which results in the production of antibodies against these antigens. In the case of a long-term disease, due to the molecular mimicry, immune system may "switch" to the production of B cells synthesizing Abs against "self" antigens [58-63, 152-156].

However, the development of MS in humans and EAE in mice is not necessarily associated with viral and bacterial infections. Ongoing apoptosis of cells in a mammalian body causes an increase in the concentration of DNA–histone complexes in the blood [157]. In addition, human blood contains free molecules of MBP and peptides from proteins of myelin sheath that envelopes nerve cells. At the early stages of MS and EAE, these molecules can penetrate through the blood–brain barrier and trigger local inflammatory processes, including induction of propagation of B cell clones producing autoreactive Abzs. Such changes in the BMSC differentiation profile can affect the repertoire of B cells synthesizing antibodies with different properties against these antigens. AIDs are known to be accompanied by the impairments

of the blood–brain barrier, which becomes permeable for various molecules, including large ones [158, 159].

MBP, histones, their fragments and complexes with DNA can bind to a variety of other proteins, nucleic acids, lipids, polysaccharides, cells, etc., at different stages of spontaneous and antigen-induced EAE development. At the same time, each stage of MS is characterized by the presence of different components in the blood. With regard to the above, different complexes of histones and MBP with DNA and other blood components can penetrate into the bone marrow liquor at each EAE stage, which must lead to changes in the BMSC differentiation profile and appearance of completely or incompletely differentiated B cells producing autoAbs and Abzs with new properties in the blood and organs. As it has been shown in [111-113], the activity of Abs hydrolyzing DNA, MBP, and oligosaccharides from the cerebrospinal fluid of MS patients was 30-60-fold higher than the activity of Abs from the blood of the same patients, which demonstrated that some lymphocytes fully differentiated already in the bone marrow. However, not all lymphocytes undergo complete differentiation in the cerebrospinal fluid; some of them are transported to organs, where they further differentiate under the influence of blood components and cells. These lymphocytes can also produce Abzs with properties other than the properties of Abzs in the cerebrospinal fluid.

Another important question is the mechanisms of formation of Abzs with the cross-catalytic activity and potential role of these Abzs in the pathogenesis of AIDs. It should be noted that Abs against various antigens can form “semispecific” complexes with compounds containing elements of structure of specific antigens. This widespread phenomenon has been named polyreactivity (or polyspecificity) of antibody complex formation [160-166]. As has been shown previously, amino acid sequences of all five histones and MBP and, especially, their antigenic determinants show a high level of homology [58-63, 106-109, 147-150]. Also, all histones and MBP contain many positively charged lysine and arginine residues. As a result, autoAbs and Abzs against five histones and MBP can form complexes with any of these proteins, thus demonstrating polyreactivity in the formation of “semispecific” complexes.

Natural Abzs are formed against specific structures of molecules that simulate transition states of chemical reactions [1-12, 58-63]. In principle, anti-protein Abzs can be formed against AGD or protein sequences simulating transition states of the peptide bond hydrolysis reaction. In proteins, sites cleaved by Abzs are located mainly in the AGDs [58-63]. There are 3 to 11 different AGDs identified for each histone [167-170], while MBP has 4 AGDs [171]. The efficiency of formation of Abzs against different AGDs of histones and MBP significantly varies and may depend on the immunogenicity of either AGDs themselves or their complexes with other molecules [58-63]. It has been shown that the major antigens in the formation of Abs against histones and DNA are DNA-histone complexes that appear in the blood as a result of apoptosis [157]. However, MBP also effacingly forms complexes with DNA [164]. Therefore, different autoAbs and Abzs can be formed against individual histones or protein complexes, as well as their associates with DNA and other molecules. Abzs against MBP and MBP–DNA complexes can also differ. According to the data of some studies, AGDs of histones and MBP can significantly vary in the efficiency of formation of Abzs against their protein sequences [58-63, 146-150]. At the same time, due to the formation of complexes of individual histones and histone complexes with different blood molecules typical of different EAE stages, some AGDs can be less immunogenic, while other AGDs or even other histone and MBP sequences can become more accessible and immunogenic, i.e., can better simulate transition states of peptide bond hydrolysis reaction. Recently, it has been shown that new AGDs can form at the interfaces between histones and DNA, so that the immune response against such complexes can result in the formation of Abzs hydrolyzing both DNA and histones [136].

Therefore, at different EAE stages, all histones, MBP, and their complexes can provide different fragments of protein sequences that would simulate transition state of peptide bond hydrolysis for further Abz formation. As a result, anti-histone or anti-MBP Abzs formed at different EAE stages can target different sequences of these proteins and their complexes, which might be the major cause of significant differences in the number and type of hydrolyzed sites for Abzs generated during spontaneous and antigen-induced development of EAE.

The high frequency of occurrence of catalytic antibodies is due to several reasons. Immunization of AID-prone mice with antigens results in a significant expansion of Abz repertoire compared to non-autoimmune mice [165, 166]. This is due to the fact that immunization causes changes in the BMSC differentiation profile with the expansion of autoreactive B cell clones producing Abzs only in mice prone to AIDs [38-63, 104, 105], but not in normal mice [104, 105]. The appearance of Abzs with a lower activity in the blood of normal mice might be associated with the differentiation and enhanced proliferation of lymphocytes in the blood, thymus, lymph nodes, spleen, and other organs [104, 105]. The appearance of Abzs with the cross-enzymatic activity, e.g., capable of hydrolyzing both histones and MBP, is caused by a high level of sequence homology of these proteins.

CONCLUSIONS

At present, many questions remain about the mechanisms of progression of autoimmune and neurological diseases and possibilities of immune response to different antigens in these pathologies. Theoretically, human immune system is capable of synthesizing about a million types of Abs with different properties against the same antigen. It is still unknown how many Abs and with what properties can be formed in healthy people and patients with various diseases. Analysis of monoclonal Abs obtained by the phage display technique has shown that the number of Abs against DNA and proteins in the blood of patients with SLE can be more than 3-4 thousand, and approximately 30-40% of them are Abzs hydrolyzing DNA and MBP. This review presents the first analysis of the role of the BMSC differentiation in the progression of multiple sclerosis and SLE and formation of B cells producing Abzs harmful for mammals. It has been shown that Abzs against five histones hydrolyzed each of these histones and MBP, while anti-MBP Abzs hydrolyzed MBP and all five histones. It was also established that the substrate specificity of Abzs in the hydrolysis of histones and MBP significantly varied depending on the MS or SLE stage. The review presented for the first time the data on the exceptional diversity of autoAbs and Abzs and their biological functions, as well as discussed their role in the pathogenesis of AIDs.

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