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Mechanisms of autoimmune diseases development

Experimental autoimmune encephalomyelitis (EAE)-prone C57BL/6 and systemic lupus erythematosus MRL-lpr/lprmice were used as models of human autoimmune diseases (AIDs). It was shown that the development of these AIDs associated with changes in bone marrow lymphocyte proliferation and differentiation profiles of hematopoietic stem cells.In parallel these changes result in an increase in proteinuria, titers of auto-antibodies against DNA, myelin basic protein (MBP) and mouse peptide MOG_{35-55}, as well as in the increase in antibodies catalytic activities in the hydrolysis of DNA, MBP, and MOG_{35-55}. It was shown that the mechanisms of the development of the EAE and SLE are very similar.

Key words: EAE model, C57BL/6 mice; catalytic antibodies; colony formation; hematopoietic progenitors; lymphocyte proliferation; apoptosis in different organs

Multiple sclerosis (MS) is known as the inflammatory and demyelinating disease of the central nervous system (CNS), and perivascular infiltrates composed largely of macrophages and T lymphocytes [8]. Numerous studies support an important role of autoimmune reactions in the destruction of myelin, while the precise reason of MS remains unknown. Data indicates that activated myelin-reactive $CD4^+$ T cells may be principal mediators of MS. Several recent findings also specify an important B cells role and autoantibodies (auto-Abs) against autoantigens of myelin in the MS pathogenesis. It was shown, that antibodies from sera of MS patients hydrolyze myelin-basic protein (MBP), DNA, and polysaccharides [8, 11, 12]. It was shown that the relative activities of IgGs in the hydrolysis of MBP, DNA, and oligosaccharides from the cerebrospinal fluid of MS patients are on average from 50 to 60-fold higher than Abs from the sera of the same patients [3, 4, 9].

Systemic lupus erythematosus (SLE) is one of several AI diseases with increased level of anti-DNA Abs, DNase and RNase Abzs possessing highest catalytic activities and broad substrate specificity [5, 7, 10]. Many SLE anti-DNA Abs are directed against histone-DNA nucleosomal complexes appearing as a result of internucleosomal cleavage during apoptosis. Apoptotic cells are the primary source of antigens and immunogens in SLE, and these features in recognition, perception, processing, and/or presentation of apoptotic auto-antigens by antigen-presenting cells can cause autoimmune processes [5, 7, 10].

Experimental autoimmune encephalomyelitis (EAE)-prone C57BL/6 mice are known as a model of human multiple sclerosis [2, 6, 8], while MRL-lpr/lprmice is model of human systemic lupus erythematosus (SLE) [1,10] MRL-lpr/lprmice are characterized by marked hypergammaglobulinemia, production of numerous auto-Abs, circulating immune complexes, glomerulonephritis and severe lymphadenopathy. A mutation in the *lpr* gene of these mice leads to a deficit in functional Fas ligand and dysregulation of apoptosis in homozygotes. As a result, the mice develop SLE-like phenotype, including accumulation of double-negative T cells ($CD4^-$ $CD8^-$ $B220^+$ TCR^+) in peripheral lymphoid organs [1, 10].

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ImmunizationMRL mice with DNA and C57BL/6 mice with MOG, DNA-histones, and DNA-methylated bovine serum albumin (met-BSA) complexes results in similar effects on the bone marrow lymphocyte proliferation and differentiation profiles of hematopoietic stem cells as well as on the level of cell apoptosis in mice bone marrow and other organs [1]. Anti-DNA antibodies are usually directed against histone-DNA complexes resulting from cell apoptosis. Immunization of EAE mice with MOG_{35-55} results at acute phase of EAE development (7-20 days) in the production of catalytic antibodies hydrolyzing efficiently myelin basic protein (MBP), MOG, and DNA with parallel suppression of antibodies hydrolyzing histones (Fig. 1) [2, 6]. In contrast to MOG, immunization with DNA complex with methylated bovine serum albumin (DNA-met-BSA) and histone-DNA results in the proteinuria suppression, a significant increase in the titers of antibodies against DNA, MBP, MOG as well as their catalytic activities in the hydrolysis of these antigens, but slightly changesthe concentration of cytokines [2, 6]. In contract to MOG, DNA-histone and DNA-met-BSA stimulated the formation of anti-DNA antibodies hydrolyzing DNA with a long delay (15-20 days) (Fig. 1).The data indicate that for C57BL/6 mice, different complexes of DNA with met-BSA and histones demonstrate antagonistic effects compared with MOG. DNA-histones stimulate the appearance of histones-hydrolyzing abzymes in the acute EAE phase, while with DNase activity only in significantly late period. The data shows that MOG,histone-DNA, and DNA-met-BSA have different effects on many bone marrow, cellular,immunological, and biochemical parameters of immunized mice, but all antigens finally significantly stimulate the development of the EAE.

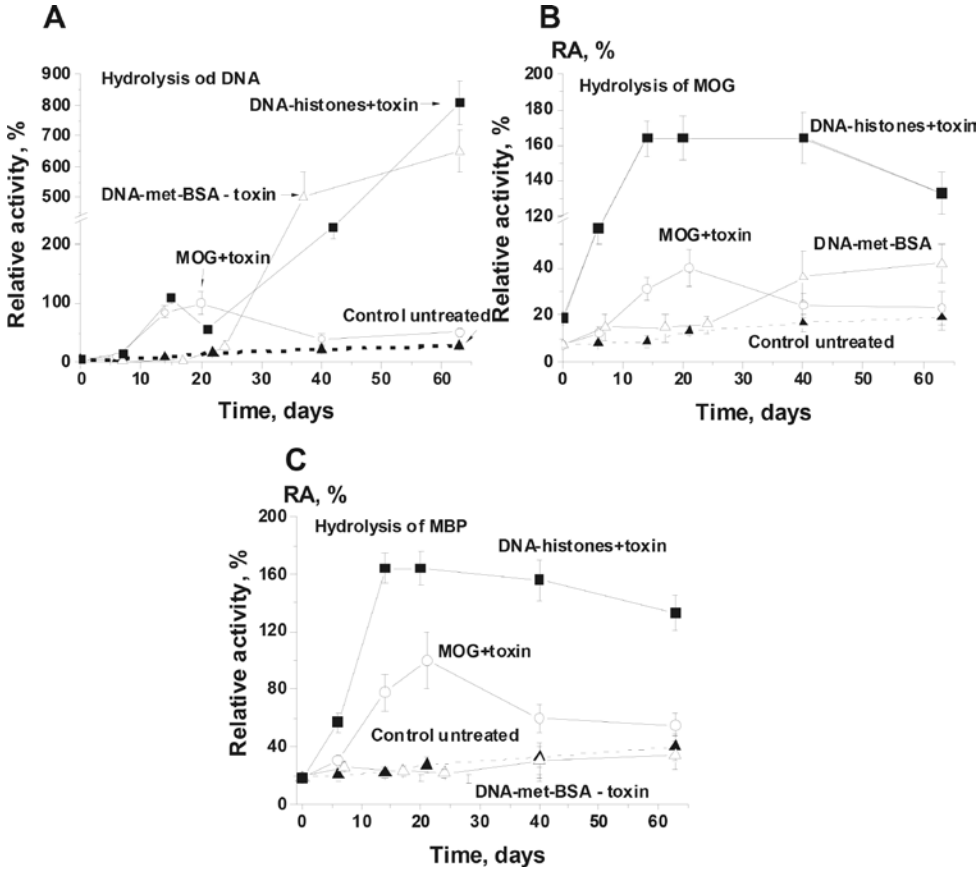

Fig. 1. Relative activities of IgGs in the hydrolysis of DNA (**A**), MOG- (**B**) and MBP (C). The in-time changes in average values of relative activities (RAs) for IgGs of different mouse groups (each group made up of 7 mice) after their treatment with different antigens are shown on panels A-C. The error in the values determined from two experiments conducted for each mouse for all groups did not exceed 7–10%

On the whole, the mechanisms SLE and EAE development have much in common and are clearly associated with the bone marrow differentiation profiles of hematopoietic stem cells and increase in lymphocyte proliferation (Fig. 2).

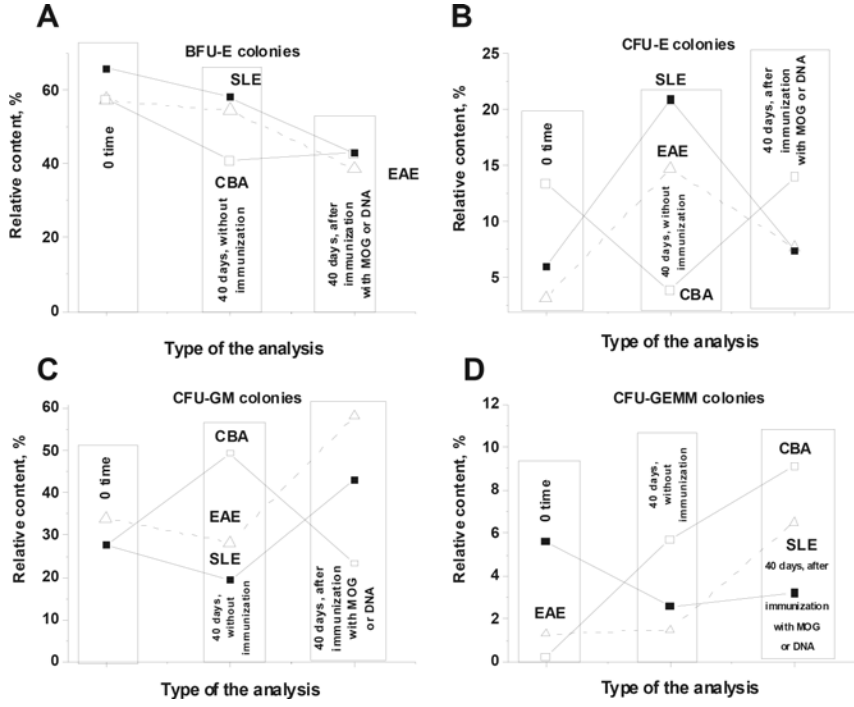

Fig. 2. Change in the relative percent (sum of four types of colonies was taken for 100 %) of BFU-E (A), CFU-E (B), CFU-GM (C), and BFU-GEMM (D) types of colonies in comparison with zero time of the experiments (first group of values) in the case of spontaneous development of EAE and SLE by respectively C57BL/6 and MRL-lpr-lpr mice after 40 days and changes of differentiation profile of HSCs in CBA mice after 40 days (second group of values); third group of values corresponds to relative amount of the colonies after 40 days in the case C57BL/6 and CBA mice treated with MOG and MRL-lpr-lpr mice immunized with DNA [8]

Fig. 2 demonstrates the relative levels of BFU-E, erythroid burst-forming unit (earlyerythroidcolonies); CFU, colony-forming units; CFU-GM, granulocytic-macrophagic colony-forming unit, CFU-E, erythroid burst-forming unit (late erythroidcolonies) CFU-GEMM, granulocytic-erythroid-megacaryocytic-macrophagic colony-forming units (%) at beginning (zero time), spontaneous changes and after mice treatment with MOG (57BL/6) and DNA (MRL-lpr-lpr) at 40 days of the experiments. One can see that the relative content of BFU-E colonies (%) constantly decrease in autoimmune EAE and SLE mice at transition from zero time to spontaneous development of these diseases (40 days) and acceleration of their development by treatment with MOG and DNA at 40 days (Fig. 2A). Non-autoimmune CBA mice demonstrate at 40 days a decrease in the percent of BFU-E, when their treatment with MOG leads to remarkable increase in the relative number of these cells. Very similar regularities in the changes of the relative content of CFU-E (Fig. 2B) CFU-GM (Fig. 2C) are observed for EAE and SLE mice and they are directly opposite than that for the CBA mice. There is a remarkable but not essentially important difference in the curves corresponding relative number of CFU-GEMM colonies for EAE and SLE mice, but they are very different to that for CBA mice (Fig. 2D). Thus, it is obvious that over time some changes in the profile of stem cells differentiation can occur in the case of non-autoimmune and autoimmune mice. However, these changes are very different or even opposite for non-autoimmune and autoimmune mice during their growth

(CBA) or spontaneous development of ADs (SLE and EAE) as well as after immunization of mice with different specific stimulators of autoimmune processes. It was shown that SLE and EAE pathologies in two different autoimmune lines of mice on overall demonstrate very similar regularities of change in differentiation profiles of bone marrow stem cells, which lead to the production of catalytically active antibodies harmful for mammals. It seems reasonable to believe that additional amiss differentiation of lymphocytes happens not only in different organs but already at the level of the bone marrow where the formation of cells producing auto-Abs and abzymes results in the increase in enzymatic activities of abzymes comparing with blood sera.

Overall, the data obtained for experimental mice (models of human SLE and multiple sclerosis), and analysis of patients with SLE and multiple sclerosis testify that the mechanisms of the development of these pathologies in both case are very similar.

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