4

The Experimental Model of the Autoimmune Glomerulonephritis Induced by the Chronic Graft versus Host Reaction

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1. Introduction

Graft-versus-host reaction (GVHR) is a cellular immune reaction developed by transplanting mature T-lymphocytes to tissue incompatible recipients. As it has been stated by R.E. Billingham in a Harvey Lecture, there are three requirements for the development of GVHR: the graft must contain immunologically competent cells; the recipient must be incapable of rejecting the transplanted cells; the recipient must express tissue antigens that are not present in the donor (Billingham, 1966, as cited in Sun et al., 2007). There are several situations in which it's possible: the introduction of incompatible lymphocytes to newborn or adult immunocompromised recipients or the transfer parental lymphocytes to F1 hybrids. A recipient with a normal immune system will usually reject cells from a foreign donor.

At the present time there are described and characterized two forms of graft-versus-host reaction: acute and chronic. The mechanisms of acute and chronic GVHR are distinguished by participating of $CD8^+$T-cells. If the $CD8^+$T-cells are involved in the development of immune processes, a primary stimulating phase of reaction (activation of the donor cell by recipient alloantigens) is followed by a cytotoxic phase including a generation of effector cells – cytotoxic T lymphocytes (CTL), directed against recipient alloantigens, and the reaction ends with destruction of host tissues. In general, it can be called a normal physiological immune reaction "graft versus host" – accomplished immune response of mature donor cells against allogeneic recipient. From this viewpoint chronic GVHR is an incomplete ("defective") GVHR: the reaction does not lead to formation of $CD8^+$T-effector cells and to a development of a cytotoxic phase, as it should be, but «freezes» at a primary stimulating stage and ends with lymphoproliferation. Such type of the reaction may be caused by different situations: removal or inactivation of some inoculum T cells subpopulations, the suppression of the reaction by pharmacological agents at early stages, or the lack of donor T cells stimulation through the absence of MHC class I incompatibility.

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Acute GVHR leads to severe cytotoxic reaction of transplanted cells against host tissues. It's characterized by thymic involution, pronounced hypoplasia of the lympho-hemopoietic tissue, including aplastic anemia, immunodeficiency, hypogammaglobulinemia, and sepsis. Acute GVHR often ends with the death of the recipient. Chronic GVHR is characterized by a long incubation period and relatively low mortality. It's manifested by lymphoid hyperplasia, hypergammaglobulinemia, autoantibody formation. Chronic GVHR is more diverse in the immune mechanisms and accordingly in the clinical manifestations: it may be observed the development of immunodeficiency, the formation of different variants of autoimmune pathologies, lymphoproliferative processes, skin lesions, disorders of intestines (enteritis, colitis) and other internal organs (Gleichmann et al., 1984; Via & Shearer, 1988; Mori et al., 1998; Chu & Gress, 2008).

It has been shown that GVHR may be useful model for study various human disorders. In mouse models of GVHR a reaction may be directed to MHC class I, MHC class II, or both or to isolated multiple minor histocompatibility antigens (miHA) alone. In each case the reaction is dependent on either $CD8^+$T cells, $CD4^+$T cells, or both, depending on the strain combination of donor and recipient. When donor and recipient are distinguished by MHC I and II classes acute GVHR occurs, whereas in the case of only MHC class II differences chronic GVHR is formed. Initially acute GVHR was considered Th1-dependent and chronic GVHR - Th2-dependent form of reaction (Krenger & Ferrara, 1996; Okamoto et al., 2000; Shustov et al., 2000; Kataoka et al., 2001). Now it has become evident that this is an oversimplification and a situation is much more complicated. Currently it has been shown involvement either Th1- and Th2-subpopulation in the development of acute and chronic GVHR, and thus there are many unresolved issues concerning of GVHR mechanisms and participating of different cytokines and cell subpopulations, particularly with regard to the chronic form of the reaction (Koreth & Antin, 2008; Reddy & Ferrara, 2009).

2. Experimental model of glomerulonephritis induced by chronic GVHR

Graft-versus-host reaction leads to the development of immunopathological states (graft-versus-host disease – GVHD), in some cases similar to human disease which are caused by immune abnormalities. Primarily it refers to autoimmune diseases. The transfer parental lymphocytes to F1 hybrids is particularly appealing for use as models of human diseases. In this case it does not require to expose recipients previously to irradiation or cytotoxic drugs suppressing its ability to graft reject.

In semiallogeneic system C57Bl/6→(C57Bl/6xDBA/2)F1 donor and recipient are differ in the MHC class I and II and an acute form of reaction develops in accordance with a general rule. However if cells of the second parental line DBA/2 use for transplantation (the semiallogeneic system DBA/2→(C57Bl/6xDBA/2)F1) chronic GVHD develops despite differences between donor and recipient by MHC classes I and II and miHAs (Gleichmann et al., 1984; Reddy et al., 2008; Kim et al., 2010). The inability of DBA/2 mice lymphocytes to induce acute GVHD may be explained by different production of inflammatory cytokines such as IFNγ , TNFα, IL-6, which play an important role in the activation of CTL, in mice with $H2^b$ and $H2^d$ haplotype (De Maeyer-Guignard et al., 1986; Raj et al., 1992). Moreover, it has been shown that the population of $CD8^+$lymphocytes in DBA/2 mice is quantitatively and qualitatively defective. $CD8^+$T-cells of DBA/2 mice generate a weak response to BDF1 alloantigen in vitro and the frequency of CTL precursors in DBA/2 mice is many times less

than one in C57Bl/6 mice (Via et al., 1987; Tschetter et al., 2000). Thus induction of GVHR in transfer system DBA/2→(C57Bl/6xDBA/2)F1 does not lead to an acute form as it should be due genetic donor-recipient differences but causes a chronic GVHD dependent on $CD4^+$ donor cells (Gleichmann et al., 1984; Reddy et al., 2008). There are a polyclonal activation of B cells, an increase of a total IgG level, a formation of multiple autoantibodies including antibodies to DNA. Autoantibodies found in this GVHR are of the IgG class whereas antibodies binding to a variety of self antigens and found in the peripheral blood of normal individuals are of the IgM class (Rolink et al., 1987). Chronic GVHD results in a development of autoimmune disorder similar human systemic lupus erythematosis (SLE) and in a formation of lupus-like immune complex glomerulonephritis (Via & Shearer, 1988).

2.1 Two variants of GVHD induced in transfer system DBA/2→(C57Bl/6xDBA/2)F1

Studying this model we have discovered that although the typical chronic GVHR develops in all recipients reaction can proceed in two different directions despite the genetic homogeneity of recipients - (C57Bl/6xDBA/2)F1 mice. The development of chronic GVHR is sustained by increased spleen cell number and polyclonal B-cell activation in the absence of thymus destruction (Kozlov et al., 2002). The absence of destruction of lymphoid tissue, in particular, atrophy of the thymus is a sharp-cut distinctive feature of chronic GVHD from its acute form. Chronic GVHD is not accompanied by marked disruptions of thymus tissue, infiltration of the thymus by donor T-cells, pronounced structural changes, signs of local inflammation and disorders of cell proliferation (Krenger et al., 2000).

2.1.1 Development of chronic GVHR

The formation of glomerulonephritis is going on for 6 – 12 weeks (Fig. 1). The autoimmune glomerulonephritis develops in 50-60% recipients (a *lupus* group), whereas marked disorders of kidney are absent in the rest ones (a *nonlupus* group) (Fig. 2).

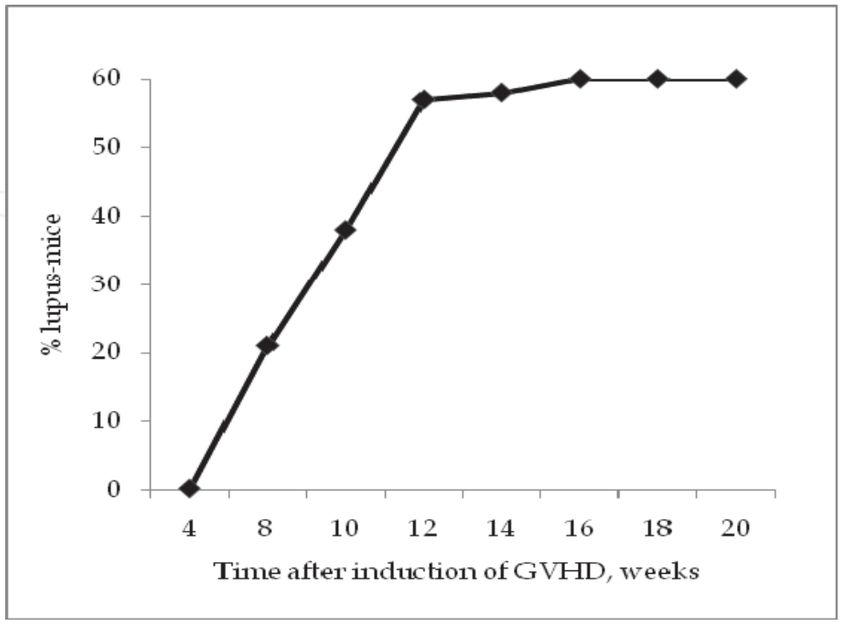


Fig. 1. Frequency of lupus-like nephritis in the course of chronic GVHD development

The availability of the autoimmune glomerulonephritis has been tested by the urine protein level that has been strictly correlated with the appearance of immune complex deposits in kidney and morphological manifestations of kidney disorders as it has been verified previously (Kolesnikova et al., 1991).
The development of the reaction is accompanied by the increase of total IgG level and the appearance of autoantibodies to own tissues components (dsDNA, erythrocytes) in the peripheral blood (Fig. 3) (Kudaeva et al., 2005a).

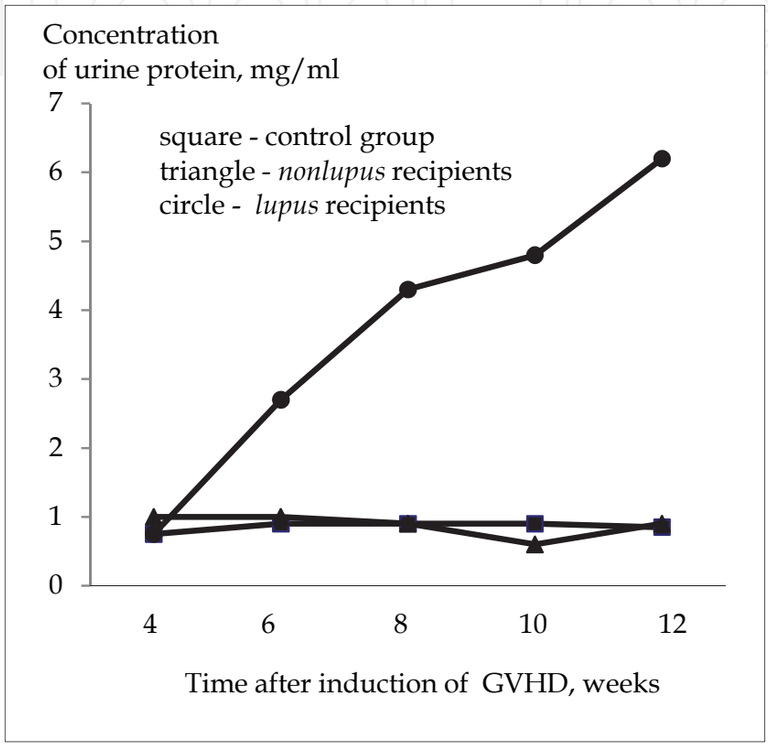
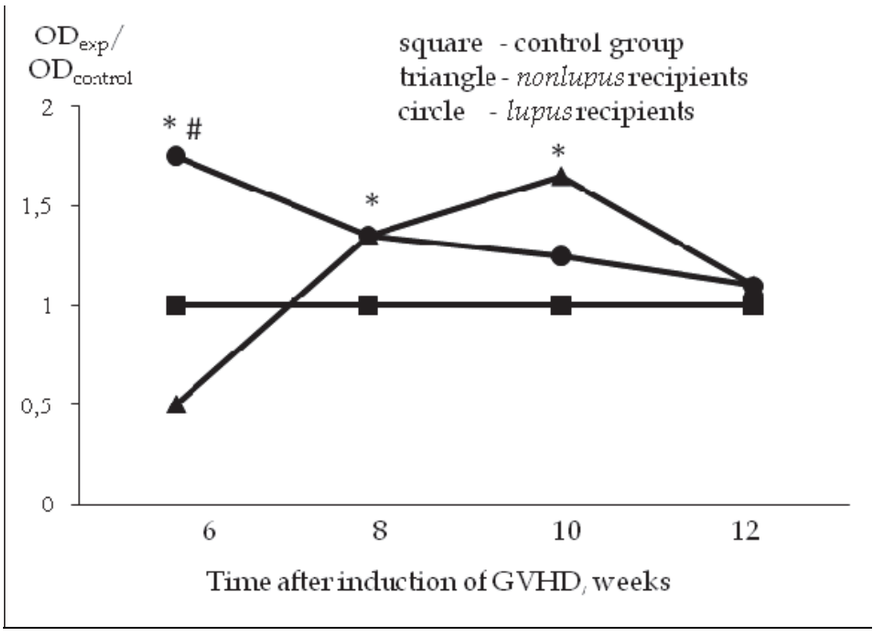


Fig. 2. Formation of glomerulonephritis in the course of chronic GVHD development

2.1.2 Kidney morphology

The severity of the pathological process in the kidneys is evaluated by a 4-marks scale depending on the number of glomeruli involved in the pathological process and the extent of their damage (Yoshioka et al., 1989; Muracami et al., 1995).
Morphological study has shown that animals without proteinuria (a *nonlupus* group) have slight pathomorphological changes in the form of proliferative mesangium in some glomeruli, expressed in increasing in the number of mesangial cells and in the size of the glomerular capillaries. A weak proliferation of mesangial cells combines with dust-like deposits of IgG in the glomeruli and small proteinosis of tubular epithelium. It is observed small periglomerular lymphoid infiltrates. The kidney structure is saved. Tubules dystrophy is absent. Morphological characteristics of renal pathology correspond to 1 in *nonlupus* recipients.
In the group of animals with proteinuria (a *lupus* group) it is observed gross changes in renal tissue. Changes in the glomeruli become diffuse and are expressed in increasing the number of mesangial cells with mesangial matrix deposition, diffuse wall thickening of

capillary loops until the hyalinosis lesions. Glomeruli become "gripping" look. Periglomerular lymphoid infiltrates meet constantly. Proteinosis of convoluted tubule epithelium is expressed sharply. In some cases there is the phenomenon of glomerular sclerosis. Deposits of IgG in the glomeruli have linear and granular character. Morphological characteristics of renal pathology correspond to 3.5 in *lupus* recipients. At 6-7 months of illness proteinuria attains a high level and coarse sclerotic changes dominate in kidney tissue: multiple sclerosis and hyalinosis of many glomeruli, proliferation of renal capsule epithelium with the formation of "crescent", expressed tubular atrophy with cystic enlargement of the lumen, lymphoid infiltration of the interstitium. It is found granular IgG deposits in sclerosal glomeruli; content of cystic tubules are positive stained for IgG also. Thus the induction of chronic GVHD in genetically identical recipients leads to the development of autoimmune glomerulonephritis in the part of the recipients.



* - p < 0.05 compared between control and experimental group; # - p < 0.05 between experimental groups

Fig. 3. The level of antibodies to dsDNA in recipients in the course of chronic GVHD development

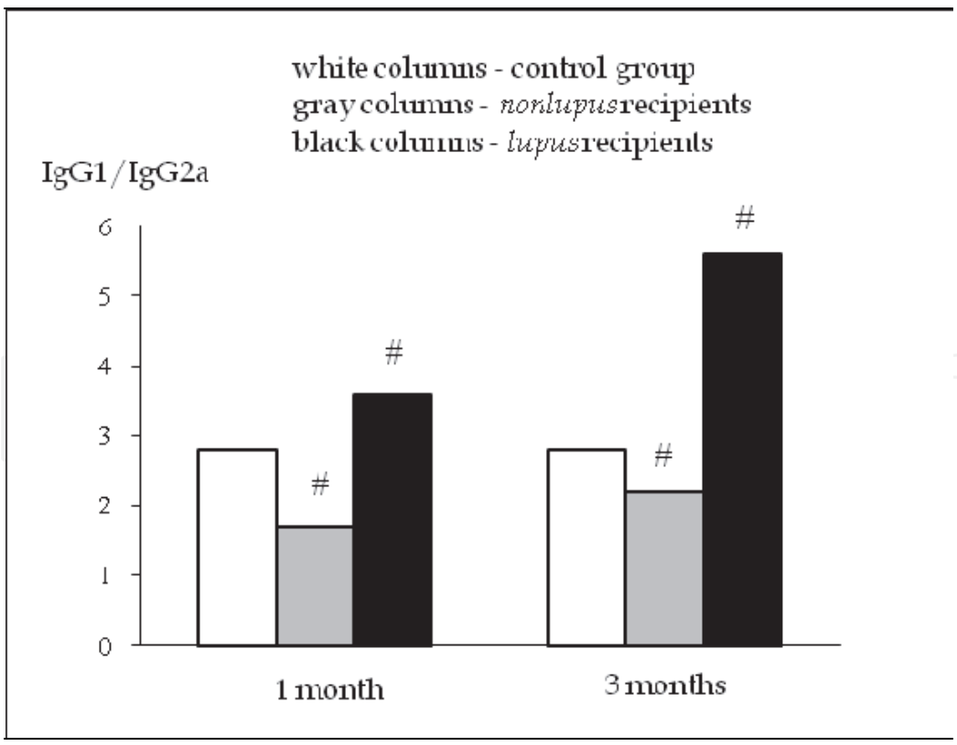
2.1.3 The Th1/Th2 balance

The further study has revealed that different Th1/Th2 ratio is the main distinction between *nonlupus* and *lupus* recipients. Existence of two Th-subpopulations producing different cytokine sets and exerting opposing influence upon basic links of immune response has been described among murine $CD4^+$T-cells in 1986 and then among human T-lymphocytes (Mosmann et al., 1986; Del Prete et al., 1991). It has led to conception of immune polarization: Th1/Th2 balance is the basic parameter of regulation of immune processes (Mosmann & Sad, 1996; Allen & Maizels, 1997; O'Gor et al., 2003). The Th-cell fate decision depends on specific Th1 or Th2 factors of transcription that is determined by a set of external epigenetic factors (Glimcher & Murphy, 2000; Wilson & Makarb, 2002; Agnello et

al., 2003). Choosing of each Th-cell differential way is subjected to influence of abundant factors connecting immune reactions with the current condition of a whole organism. The GVHD is among the processes in which Th1/Th2 balance plays the pivotal role.

Application of this paradigm for studying the regulation of immunity in both normal physiological conditions and immune pathological states has proved fruitful, and today is widely used in the study of processes such as bacterial and viral infections, allergic diseases, immune responses during carcinogenesis, autoimmune disorders, immune conflicts in pregnancy (Fresno et al., 1997; Kunzendorf et al., 1998; Chaouat et al., 2003; Wilczynski, 2005). Not all the currently known experimental facts and clinical observations perfectly fit into this concept. There are many new data on the participation of other T-cell subpopulations in the regulation of immune processes (Th17, Treg, ThF, Th9) (Mosmann et al., 2009). However the application of this paradigm remains useful to solve contemporary problems of the immune regulation.

The following points indicate that Th1- or Th2-subpopulation is predominant in *nonlupus*- or *lupus*-mice respectively (Vlasov et al., 2002; Kozlov et al., 2002; Kudaeva et al., 2005b). It is known that in mice Th1-dependent immune response is characterized by increased IgG2a subclass level, whereas activation of Th2-cells is accompanied by an increase of IgG1 one (Snapper & Paul, 1987; Morris et al., 1994). Ratio of Th1- and Th2-dependent IgG subclasses in peripheral blood of mice with GVHD shows a pronounced shift toward IgG2a (Th1-dependent subclass) in *nonlupus* mice and toward IgG1 (Th2-dependent subclass) in the *lupus* mice. Differences emerge at the early stages of reaction (1 month) and amplify over time (6 months) (Fig. 4).



- $p < 0.05$ compared between *nonlupus* and *lupus*

Fig. 4. IgG1/IgG2a ratio in the serum of mice with chronic GVHD

There are many observations about the intimate direct correlation between the concentration of IgE and the level of the key Th2-cell cytokine IL-4 (Doutrelepont et al., 1991; Umland et al., 1992; Ushiyama et al., 1995). Determination of the IgE concentration in peripheral blood of recipients has shown a high IgE level during the development of chronic GVHD and the formation of glomerulonephritis. IgE content sharply increases at the initial stages of reaction, then reduces but remains significantly higher than one of intact animals. IgE levels in *lupus* mice is considerably superior to one in *nonlupus* recipients at all stages of reaction (Tabl. 1) (Goiman et al., 2009).

	Control	*Nonlupus*	*Lupus*
10 days	6.95 (2.2 – 10.6)	20.0* (8.4 – 30.2)	24.9* (8.2 – 41.9)
24 days		132.5* (54.2 – 348.6)	232.1* (63.0 – 396.2)
3 months		24.3* # (15.0 – 36.6)	69.2* # (22.5 – 166.4)

* - $p < 0.05$ compared between control and experimental group; # - $p < 0.05$ between experimental groups

Table 1. The IgE content in peripheral blood of recipients in the course of GVHD development (M, (min-max), μg/ml)

2.2 Characteristics of recipients with glomerulonephritis

2.2.1 The homeostatic proliferation

Homeostatic proliferation is a compensatory repair of quantitative deficit of lymphocytes by triggering their proliferation at the periphery. Homeostatic proliferation decreases the variety of antigen recognizing receptors and leads to the appearance of an appreciable amount of autoreactive effector cells (Baccala & Theofilopoulos, 2005; Marleau & Sarvetnick, 2005). Now homeostatic proliferation is regarded as a possible mechanism of the development of autoimmune disease (Khoruts & Fraser, 2005; Surth & Sprent, 2008).

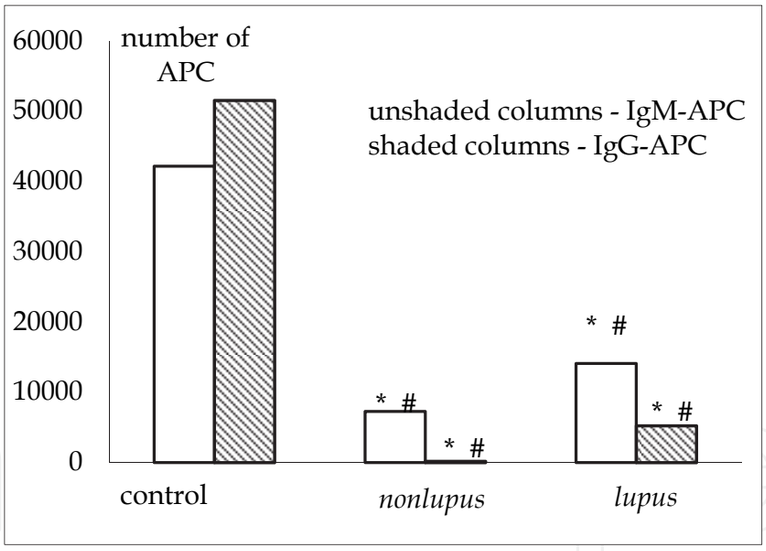
Acute GVHR is associated with a drop of lymphocyte count. Chronic GVHR is called immunostimulatory, because lymphoproliferative reaction is indicative of it (Via & Shearer, 1988). However measure of lymphocyte counts in the recipient peripheral blood over the course of reaction has revealed its drastic decrease at the early stage of chronic GVHR in this model. This decrease persists throughout the first two weeks and then is replaced by lymphocytosis followed by normalization of lymphocyte count in the peripheral blood against the background of developing splenomegaly (Tkachev et al., 2006). Hence it has been studied the possible involvement of homeostatic proliferation in the development of autoimmune disease - glomerulonephritis in this model (Goiman et al., 2010).

An obligatory condition for homeostatic proliferation of naive and memory $CD4^+$ T-cell is high concentration of IL-7 (Schluns et al., 2000; Boyman et al., 2008). It has been shown the significantly increased level of endogenous splenic IL-7 mRNA in irradiated recipients with acute GVHR (Gendelman et al., 2004). The content of IL-7 in the peripheral blood of recipients with chronic GVHR sharply increases during the early period (25.5 pg/ml) and remains high within 3 months after induction of GVHD in *lupus* recipients (6.5 pg/ml) in comparison with control animals (lower the verge of method) and *nonlupus* recipients (lower the verge of method) (Goiman et al., 2010).

The key characteristic of homeostatic proliferation is taking T memory cell phenotype ($CD4^+CD45RB^{low}$ and $CD8^+CD45RB^{low}$) by naïve T cells ($CD4^+CD45RB^{high}$ and $CD8^+CD45RB^{high}$). Despite the increase in both $CD4^+$ subpopulations (naïve and memory) its proportion is shifted towards memory cells in *lupus* recipients. The T-cell donor chimerism is just 2% in chronic GVHR in this model (Via & Shearer, 1988). Hence, the $CD4^+CD45RB^{low}$ and $CD8^+CD45RB^{low}$ cells in the spleens of *lupus* mice are mainly recipient cells.
It can be assumed that lymphopenia at the early stages of chronic GVHR causes homeostatic proliferation of T lymphocytes in *lupus* recipients, which participates in the development of autoimmune pathology in this model.

2.2.2 The immune response of recipients

GVHR is accompanied by immunosuppression. The mechanism of immunodeficiency has been well studied in case of acute reaction: it's a destruction of the recipient's immune system by donor immune cells. The mechanism of immunosuppression in the chronic form of GVHR remains unclear (Kimura & Gleichmann, 1987; Haridas & Kamat, 1997; Kataoka et al, 2001; Chu & Gress, 2008).
In spite of the occurrence of two different variants of chronic GVHR in this model the suppression of primary immune response to T-dependent antigen is observed in all recipients (Fig. 5) (Kozlov et al., 2002; Kudaeva et al., 2010b). The decrease of the primary response is significantly heavier in *nonlupus* recipients.



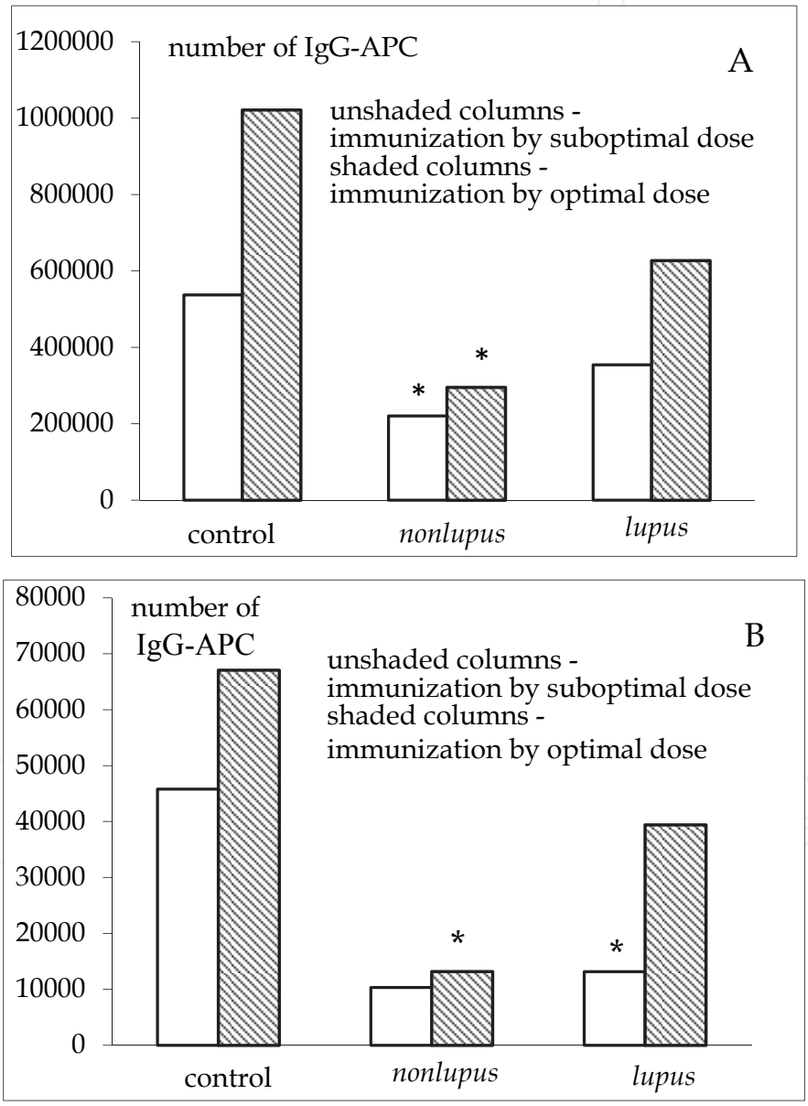
* - $p < 0.05$ compared between control and experimental group; # - $p < 0.05$ between experimental groups

Fig. 5. The level of primary humoral immune response in recipients with chronic GVHD

An enhancement of the suppressive activity of regulatory T cells, a disruption of the antigen-presenting cells, an increase of specific Th-cells apoptosis are considered as a possible reasons. Experiments in vitro indicate the possible inability of B lymphocytes in chronic GVHR to respond to T-dependent antigen. The latter can be explained by the abundance of activating factors leading to the ultimate differentiation of the few antigen specific B-cell and thus excluding its proliferation (Kimura & Gleichmann, 1987).

The inhibition of humoral immune response may be due to hyperactivation of the B-lymphocytes. Indeed, the development of chronic GVHD is accompanied by a marked polyclonal activation of B-lymphocytes, which is known to impede an adequate response to new stimulus (Reina-San-Martin et al., 2000; Spera et al., 2006; Montes et al., 2007; Marques et al., 2008).

At the same time a decrease of the secondary immune response is less marked especially in the *lupus* recipients (Fig. 6). Perhaps, it indicates that a formation of immune memory is more rigidly processes, resistant to the action of various factors. Explanation of this discordance between the level of primary and secondary response under chronic GVHD requires further investigation.



* - $p < 0.05$ compared between control and experimental group

Fig. 6. The level of the secondary humoral immune response in recipients with chronic GVHD (A – spleen; B – bone marrow)

The suppression of humoral immune response to T-dependent antigen is observed in all recipients (*nonlupus* and *lupus*) and by this means is not specific feature of autoimmune disorder in this model.

2.2.3 Anemia

Hematological abnormalities are common in systemic lupus erythematosus and may be manifested in anemia of different pathogenesis. In SLE many factors are produced which disturb the hematological balance both on the peripheral level and in the bone marrow. It is assumed that the autoantibodies produced in SLE are the main cause of autoimmune hemolytic anemia. However it should be considered that quantitative changes in the number of erythrocytes observed in this disease are also caused by chronic inflammatory condition, which impairs the endocrine function of the kidneys in erythropoietin production as the element of autoimmune disease.

Parameters	control	*lupus*
Hemoglobin, g/l	199.5 ± 3.5	137.3 ± 6.9 **
Hematocrit, per cent	49.2 ± 0.4	39.7 ± 1.4 **
Reticulocytes, pro mille	10.0 ± 1.3	26.2 ± 4.7 **

M±m, * - $p < 0.05$ and ** - $p < 0.01$ compared between control and experimental group

Table 2. Hematological parameters of *lupus* mice

It has been shown that acute GVHD (C57BL/6→(C57BL/6xDBA/2)F1) reduces the peripheral blood cell counts, the number of bone marrow cells, and colony forming unit-granulocyte macrophage (CFU-GM), whereas the host hematopoiesis in chronic GVHD (DBA/2→(C57BL/6xDBA/2)F1) is not affected within 2 weeks after the transfer of parental splenocytes (Mori et al., 1998). However study of the host hematopoiesis at late stages of GVHD has revealed the set of immune- and hemopoiesis disorders (Kozlov et al., 1995).

The results presented in Table 2 show that *lupus* mice have a significant decrease of hemoglobin and hematocrit levels in comparison with intact animals. Marked reticulocytosis corresponds to the expression of anemic syndrome and gives evidence of a quite regenerative ability of the *lupus* bone marrow. To clarify the nature of anemia assessment of early and late erythropoietic progenitors has been studied. Data on the number of erythroid precursors in the myelogram and the number of erythroid burst forming units (BFU-E) and colony forming unit-granulocyte macrophage in bone marrow are shown in Table 3.

Parameters	control	*lupus*
Nucleated erythroid precursors, per cent	28.3 ± 1.2	37.6 ± 2.9 *
BFU-E per 10^5 bone marrow cells	7.8 ± 0.9	21.3 ± 1.8 **
CFU- GM per $5x10^4$ bone marrow cells	8.7 ± 0.7 (10)	4.7 ± 0.5*

M ± m, * - $p < 0.05$ and ** - $p < 0.01$ compared between control and *lupus*

Table 3. Assessment of erythropoiesis at the level of early and late hematopoietic precursors in *lupus* mice

Changes in bone marrow smears of SLE patients with autoimmune hemolytic anemia and ones of *lupus* recipients are similar. The relative and absolute number of BFU-E in the bone marrow increases in *lupus* recipients compared with intact animals.

The decrease of hemoglobin and hematocrit in *lupus* recipients is accompanied by reticulocytosis and hypertrophy of erythropoiesis in the bone marrow, thus it becomes apparent that anemia develops as a result of increased destruction of erythrocytes.

Increasing the number of BFU-E and nucleated erythroid precursors suggests hypertrophy of erythron in *lupus* mice. Similar changes of erythron are observed in mice NZB, whose autoimmune hemolytic anemia is accompanied by increased numbers of early erythroid precursors in the bone marrow and spleen (Orlovskaja & Kozlov, 2001).

Autoimmune hemolytic anemia is diagnosed in the presence of variable intensity of anemia (usually macrocytic), reticulocytosis, and a positive direct and/or indirect antiglobulin test after ruling out other types of hemolytic anemia.

Coombs test (direct antiglobulin test) is used to verify the occurrence of erythrocyte-bound antibodies which mediate red cell destruction in anemic mice. Autoantibodies to erythrocytes have been determined by this test at weekly intervals, starting at week 1 and lasting until week 12 after the initiation of the GVHR. Coombs-positive erythrocytes begin to appear at early stages of reaction. It has been established that the frequency of Coombs-positive results within 1-2 months after induction of GVHD achieves 60%. In mice with positive results of Coombs-test hematocrit is reduced by 26%, hemoglobin by 33%. Immune complex glomerulonephritis develops in 52% of mice with positive Coombs test at the early stages of GVHR. However a positive direct antiglobulin test alone is not sufficient to diagnose of autoimmune hemolytic anemia and may be positive in many patients without anemia or negative in some patients with one.

It has been studied the possibility of correction of impaired erythropoiesis by hypoxia (Table 4). Hypoxia has had favorable effect on anemia, significantly increasing hematocrit and hemoglobin levels and reducing the increased number of reticulocytes (Kolesnikova et al., 2001).

Parameters	control		*lupus*	
	intact	hypoxia	without hypoxia	hypoxia
Hemoglobin, g/l	197.5 ± 3.5	224.5 ± 7.8	137.3 ± 6.9**	186.0 ± 4.6##
Hematocrit, per cent	49.2 ± 0.4	50.0 ± 1.3	34.2 ± 0.9 **	39.5 ± 0.9 #
Reticulocytes, per mille	10.0 ± 1.3	-	26.2 ± 4.7 **	12.3 ± 1.1##

(M ± m, ** - $p < 0.01$ compared between control and *lupus*, # - $p < 0.05$ and ## - $p < 0.01$ compared between *lupus* without hypoxia and *lupus* with hypoxia

Table 4. The influence of hypoxia on hemoglobin and hematocrit levels, reticulocyte number in *lupus* mice

It is known that hypoxia stimulates the production of erythropoietin by kidney. It is used for treatment anemia with a decrease of erythropoiesis (Eckardt et al., 1989). There are no available data on the use of chronic hypoxia for treatment of moderate hemolytic anemia with increase of bone marrow erythropoiesis combined with immunopathology. In this model it has been shown some positive effect of chronic hypoxia on GVHR induced

immunopathology: hypoxia increases humoral immune response, abolishes anemia and corrects of early and late committed hemopoietic precursors number (Kolesnikova et al., 2001). Apparently initial increase of erythropoietin synthesis leads to the growth of hemoglobin level in blood. When a level of hemoglobin in blood is restored, the hyperplasia of bone marrow hemopoietic cells stops.

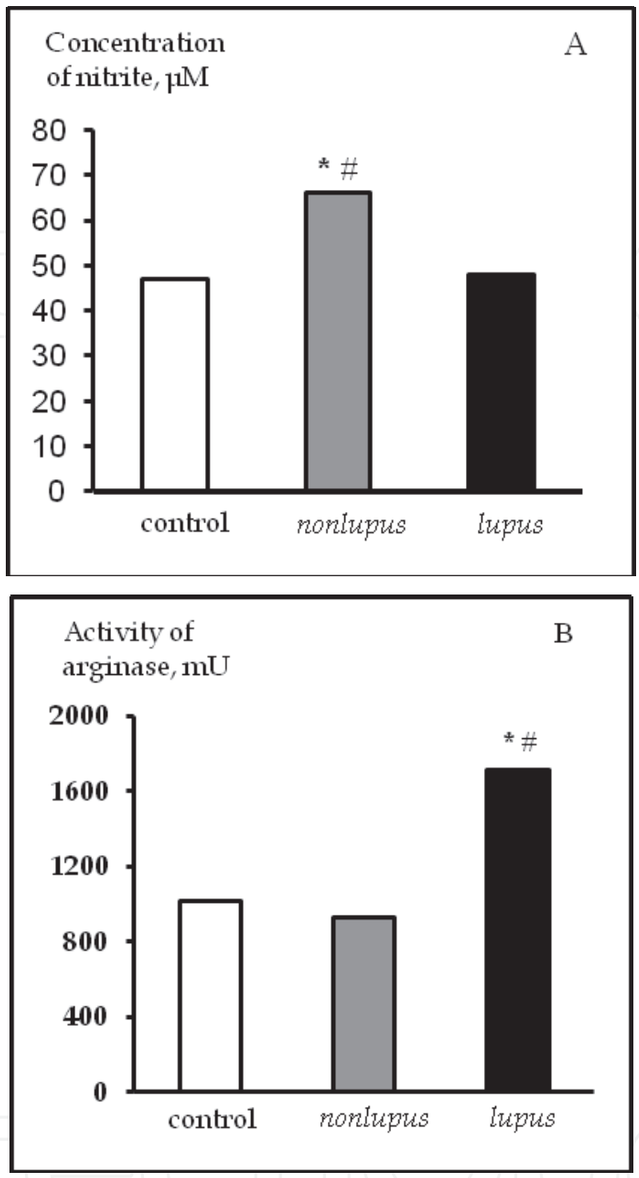
2.2.4 Macrophages

Macrophages play a pivotal role in development of immune response and inflammatory reactions, acting as effectors and regulatory cells. Their participation in renal development, damage and repair has been well described (Williams et al., 2010). In pathogenesis of immune-mediated kidney injury different types of macrophages take part. There are resident renal macrophages (mesangial cells), macrophages differentiated from blood monocytes migrating in site of inflammation, and macrophages located in other organs (e.g. spleen and lymph nodes macrophages).

Resident renal macrophages are supposed to play protective role in mechanism of glomerular damage induced by immune complexes via scavenging and preventing immune complexes depositions in glomeruli. This "physiologic" clearance of immune complexes is nonphlogistic and does not lead to increased production of inflammatory mediators (Duffield, 2003; Serhan & Savill, 2005; Bergtold et al., 2006; Castano et al., 2009). But if these mechanism is overwhelmed it results in deposit formation on glomerular basal membrane causing leukocytes activation, liberation of cytotoxic and chemoattracting products, local kidney injury and recruitment of further leukocytes (Gomez-Guerrero et al., 2004, 2005; Berger & Daha, 2010). These processes contribute a progressive loss of renal functions.

Severity of clinical manifestation of kidney diseases closely correlates with intensity of macrophages infiltration (Van Goor et al., 1994; Duffield, 2010). Transfer of semiallogeneic lymphoid cells from DBA/2 mice to (C57Bl/6xDBA/2)F1 hybrids leads to rapid accumulation of CD11a-positive leukocytes in renal glomeruli which is maximal within 4 weeks after GVHD induction and is synchronized with the time of proteinuria onset (Kootstra et al., 1998). Moreover in the murine model of proliferative glomerulonephritis caused by deposition of immune complexes at the glomerular basal membrane it has been shown that macrophages ablation ameliorates severity of injury (Guo et al., 2009).

Role of macrophages in kidney injury and repair can also depend on the mechanism of their activation. It is suggested that macrophages can polarize and differentiate into different subpopulations of activated cells according to a type of stimuli. In common, polarized macrophages can be divided into 2 basic groups: classical activated macrophages (they are named M1 cells, reminiscent of T-lymphocyte subsets) differentiate by Th1-associated cytokine IFNγ and microbe component such as LPS and alternatively activated macrophages (M2) including subpopulations of M2a (activated by Th2-dependent cytokines IL-4 and IL-13), M2b (activated via FcR) and M2c (requiring IL-10, TGFβ or glucocorticoids). These subpopulations of activated and polarized macrophages have different phenotypes and spectrum of secreting chemokines/cytokines (Martinez et al., 2008, 2009; Gordon & Martinez, 2010) and play different roles in mechanism of immunologic inflammation of the kidney (Williams et al., 2010). It is commonly accepted that M1 cells producing large amount of nitric oxide and reactive oxygen species by NO synthase and NADPH oxidase, respectively, mediate renal tissue damage while M2 cells producing significant amounts of proline and polyamines stimulate cells proliferation and sclerotic processes.



* - p < 0.05 compared between control and experimental group; # - p < 0.05 between experimental groups

Fig. 7. Activity of NO synthase (A) and arginase (B) in recipients

It is established that M1 and M2 cells are significantly differ from each other by the ways of arginine metabolism, which is a substrate of both NO synthase and arginase. M1 macrophages are characterized by high production of NO in combination with low activity of arginase, while for M2 it is typical an inverse relationship, since the balance in this subpopulation of macrophages shifts toward the reaction catalyzed by arginase (Munder et al., 1998). Thus determining the ratio of NO synthase and arginase activities in the culture of macrophages can evaluate the M1 and M2 subpopulations balance and its changes under influence of various agents.

Study of arginine metabolism in peritoneal macrophages of recipients has been shown that macrophages isolated from *lupus* mice expose high arginase activity and macrophages isolated from *nonlupus* mice without clinical symptoms of kidney disease produce large amount of nitric oxide upon LPS/IFNγ stimulation (Fig. 7).
According their metabolic properties it has been supposed that Th1-dependent variant of chronic GVHD is associated with classical macrophages activation with NO synthase prevalence, while Th2-dependent variant of chronic GVHD is characterized by alternative macrophages activation with arginase domination. Since it has been researched on peritoneal macrophages not directly involved into renal inflammation, these differences of arginine metabolism have systemic nature and may characterize metabolic changes in whole immune system. Preferential activation of M1 or M2 cells may be one of the key points of chronic GVHD-induced immunopathological processes. In Th2-associated type of chronic GVHD there are immune complexes forming deposits in renal glomeruli and causing their inflammatory damage. In this case high arginase activity of M2 macrophages can promote via enhanced polyamine synthesis the proliferation of polyclonally activated B cells and the increase of autoantibody production. Moreover, the local increase of arginase activity in renal macrophages (mesangial cells) contributes proliferative forms of glomerulonephritis and amplifies collagen synthesis causing glomerular sclerosis. It have been also shown that lowering of local NO production in glomeruli exacerbates renal injury induced by different ways and enforces proteinuria via glomerular hemodynamics disturbances (Cattell, 2002; Waddington, 2002). Controversially, high activity of macrophagal NO synthase decreases proliferation of T- and B-lymphocytes and amplifies activated cells apoptosis preventing autoimmunity expansion (Kim et al., 1999; Hoffman et al., 2002; Koide et al., 2003).

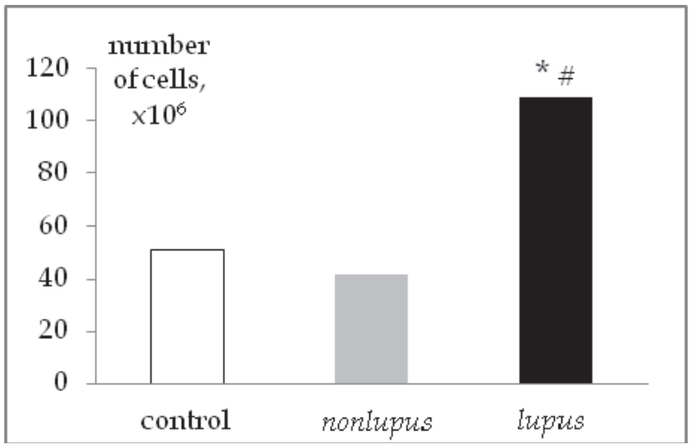
2.2.5 Cytokines

The key cytokines for Th1 and Th2 subpopulations are IFNγ and IL-4, relatively. Unfortunately, its concentrations have fallen outside of the bottom value of used test system. The concentration of IL-10, IL-15, IL-17A has been on the verge of method sensitivity or lower also. Data on IL-7 is presented in chapter 2.2.1. Determination of cytokines content in peripheral blood has reveals the increase of IL-6 and TNFα levels in *lupus* recipients (Table 5). It has been shown that serum Il-6 and IL-10 levels increase and are closely associated with disease activity in SLE (Chun et al., 2007). Today it's known the Janus-faced role of IL-6 as pro- and antiinflammatory cytokine. IL-6 participates in the acute phase response, B cell maturation and macrophage differentiation. Furthermore it has been shown that IL-6 can promote Th1/Th2 ratio towards Th2 inducing IL-4-dependent differentiation of Th2 and simultaneously inhibiting Th1 polarization through IL-4-independent mechanism (Diehl & Rincon, 2002). Thus, the high level of IL-6 coincides with the increase of $CD19^+$ B lymphocytes in spleen of *lupus* recipients and does not contradict to shifting their Th1/Th2 balance towards Th2 (Fig. 8). TNFα is also multifunctional cytokine and is involved in the different immune processes. Except proinflammatory effects it is likewise an important factor of physiologic processes of B cells growth and activation. It has been shown that its level is increased in the blood and in the inflamed kidneys of systemic lupus erythematosus patients (Aringer & Smolen, 2003) although its role in human SLE is controversial (Aringer & Smolen, 2008; Zhu et al., 2010). The high level of TNFα likely accounts for processes of inflammation in kidney; a possible cause of its increase is discussed in chapter 2.2.6.

	IL-2	IL-6	TNFα
control	2.3 (2.0 – 2.6)	4.4 (1.6 – 9.5)	7.9 (6.0 – 10.2)
nonlupus	2.6 (2.0 – 2.9)	2.3 (0 – 4.8)	9,03 (0 – 15.7)
lupus	2.9 (2.3 – 3.6)	8.9# (0 – 17.4)	19.1*# (7.1 – 40.6)

(M, min – max; pg/ml; * - $p < 0.05$ between control and experimental group; # - $p < 0.05$ between experimental groups

Table 5. The cytokines concentration in serum of recipients



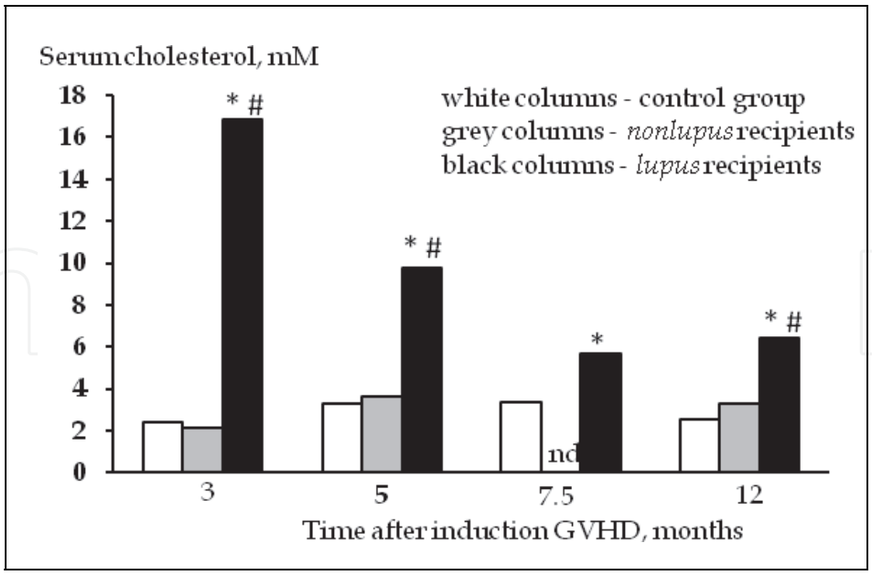
* - $p < 0.05$ between control and experimental group; # - $p < 0.05$ between experimental groups

Fig. 8. The content of $CD19^+$ cells in the spleen of recipients with chronic GVHD

2.2.6 Change of cholesterol metabolism in recipients with glomerulonephritis

The development of lupus-like nephritis in described experimental model of chronic GVHD is associated with severe hyperlipidemia (Xiao et al., 2007; Perminova et al., 2009). According to our experimental data (Fig. 9) increase of serum cholesterol level in mice with autoimmune glomerulonephritis is most pronounced in the period corresponding to the formation of kidney damage and the appearance of proteinuria (about within 3 months after induction of chronic GVHD), however, and after 5 months, and even after 12 months concentration of cholesterol in the blood of these animals remains significantly elevated. It has been also found that in these mice the triglyceride level in serum is significantly increased (from 1.72 mM in intact control to 5.25 mM in *lupus* recipients; $p < 0.01$). At the same time *nonlupus* mice have normal cholesterol and triglyceride levels. Our results of the study blood cholesterol levels in the dynamics of chronic GVHD indicate that hypercholesterolemia and formation of autoimmune glomerulonephritis occur simultaneously (Fig. 10). In the initial stages of induction of GVHD individual animals with opposite variants of the immunopathological process do not significantly differ from each other, and only after 8-12 weeks serum cholesterol level begins to increase in mice with a lupus-like nephritis. Thus, the formation of kidney damage and lipid metabolism disturbance in described experimental model are parallel to each other and appear in the same time.

The coincidence between kidney diseases and changes in lipid metabolism has been known for a long time. As stated in one of modern articles: "Historically, Virchow first suggested the association between lipids and renal disease in 1858 when he described successive stages of fatty metamorphosis and fatty detritus in the renal epithelium in Bright's disease" (Jiang et al., 2005). Now the combination of different forms of nephritis and nephrotic syndrome with hypercholesterolemia is well known in the clinic and is described in various forms of experimental nephritis in animals. It has been found experimentally that kidney disease combines not only with changes serum lipid levels, but also with a variety of disorders of lipid metabolism in tissues. In clinical and experimental works it has been evidenced that nephrotic syndrome is accompanied by significant changes in activity of some enzymes involved in cholesterol metabolism (such as HMG-CoA reductase, acyl-CoA:cholesterol acyltransferase, lecithin-cholesterol acyltransferase and other), by decreased expression of LDL receptors on membranes of hepatocytes, by decline of apolipoprotein E, and by impaired reverse cell cholesterol transport (Subbaiah & Rodby, 1994; Deighan et al., 2000; Vaziri & Liang, 2002; Shearer et al., 2005; Vaziri et al., 2011). Undoubtedly, these data are very important for deep understanding of the pathogenesis of hypercholesterolemia in nephrotic syndrome, but they do not clarify the question what are mechanisms linking kidney disease and changes in lipid metabolism. Initial assumption that the level of serum lipoproteins increases compensatory in answer to decline of serum albumin concentration, today is rejected as not supported by clinical and experimental data. It has been found that it is not correlation between serum lipid profiles and serum albumin levels while the severity of lipid abnormalities correlates with the degree of proteinuria and hence with extent of kidney damage (Vaziri & Liang, 2002; Hu et al., 2009). Thus, the question of the primary cause of the hypercholesterolemia development in renal disease remains not completely resolved.



* - $p < 0.05$ between control and experimental group; # - $p < 0.05$ between experimental groups; nd - data are not available

Fig. 9. Serum cholesterol concentrations in mice with *lupus*-like nephritis and in *nonlupus* mice

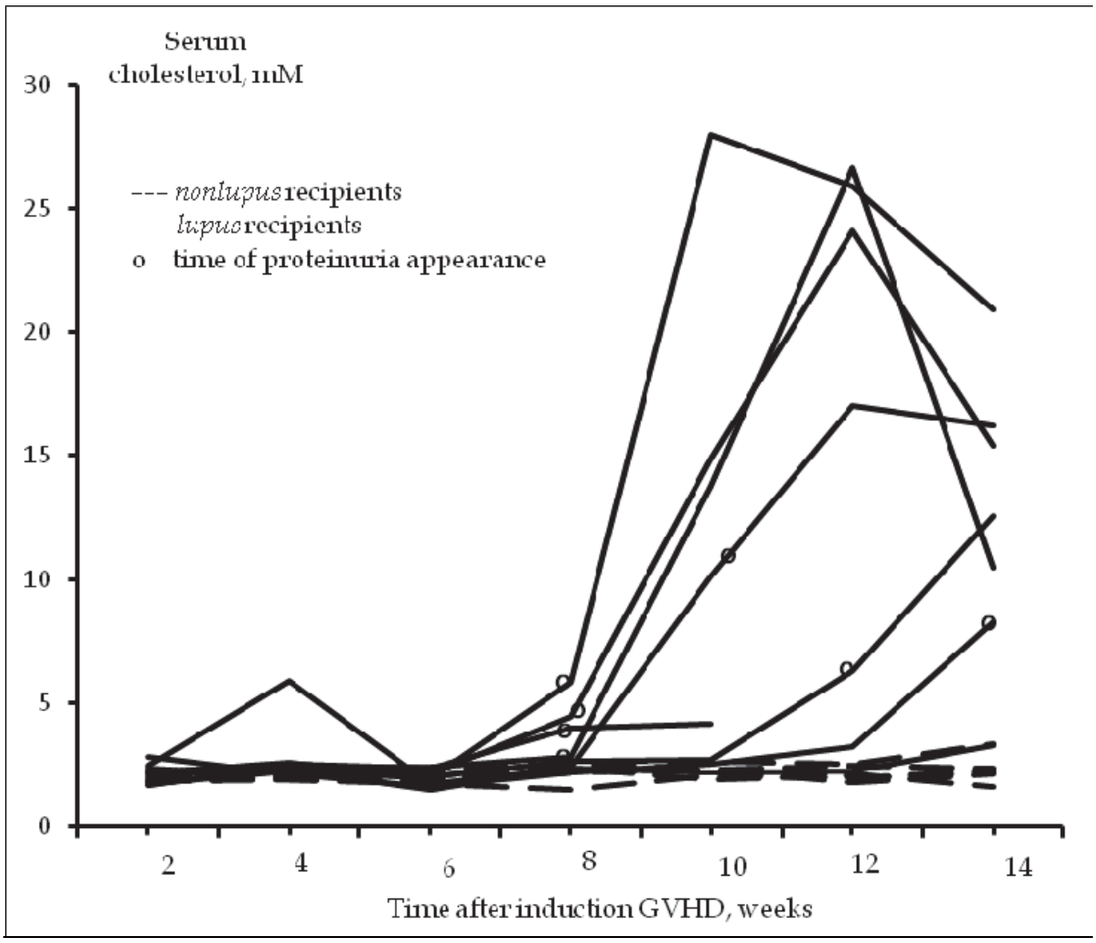


Fig. 10. Development of hypercholesterolemia in individual animals in the dynamics of chronic GVHD

It is generally accepted that the main pathogenetic point of such diseases is a massive production of specific autoantibodies and the formation of immune complexes which deposite in kidney tissues and serve as trigger for the chronic inflammatory process. In our experiments we also have found a gradual increase in the number of antibodies to DNA at the early stages of nephritis development (see 2.1.1). As it would be expected greater number of antibodies to DNA has been detected in those animals in which lupus-like nephritis develops. Based on this fact and on the currently available literary data, we assume that an accumulation of immune complexes in tissues may be act as a connecting link between kidney damage and hypercholesterolemia and that cell production of oxysterols is a key element of this association.

In vitro experiments demonstrate (Reiss et al., 2001) that adding of immune complexes to macrophages and endothelial cells inhibits the activity of mitochondrial sterol 27-hydroxylase – a key enzyme of cholesterol metabolism present in most tissues of the body and converting cholesterol to 27-hydroxycholesterol which is endogenous ligand for nuclear liver X receptors (LXRs) (Fu et al., 2001). *In vivo* this effect of immune complexes must be resulted in the decrease of 27-hydroxycholesterol concentrations in the body and therefore in the decline of the activation degree of LXRs. Since the LXR activation is associated with

the inhibition of cholesterol synthesis *de novo* and with the increase of the rate of its degradation to bile acids (Björkhem & Diczfalusy, 2002; Wang et al., 2008), reduced LXR activity would be reflected by accumulation of cholesterol in the tissues and by hypercholesterolemia. Schematic representation of these relationships is shown in Figure 11.

As of now, this assumption presents a pure speculative construction, but there are experimental evidences counting in favour of this hypothesis. In particular, it has long been known that many of the autoimmune diseases accompanied by increased formation of immune complexes are associated with pronounced hypercholesterolemia. A classical examples of such illnesses are autoimmune injuries of kidneys and systemic lupus erythematosus (McMahon & Hahn, 2007). According to literary data, the close relation between accumulation of immune complexes in tissues and hypercholesterolemia is the characteristic feature of the murine lupus-like syndromes developing spontaneously in (NZB x NZW)F1 mice, in MRL/lpr, BXSB and other relevant mouse strains (Ogura et al., 1989; Itoh et al., 1994; Gu et al., 1999; Kono et al., 2000; Lawman et al., 2004). Similar association has come to light also in experimental investigations of a various immune complex renal injuries induced in animals by the administration of $HgCl_2$, cationic bovine serum albumin and antibodies to renal proteins (Couser et al., 1978; Bagenstose et al., 1999; Shi et al., 2005; Wu et al., 2008).

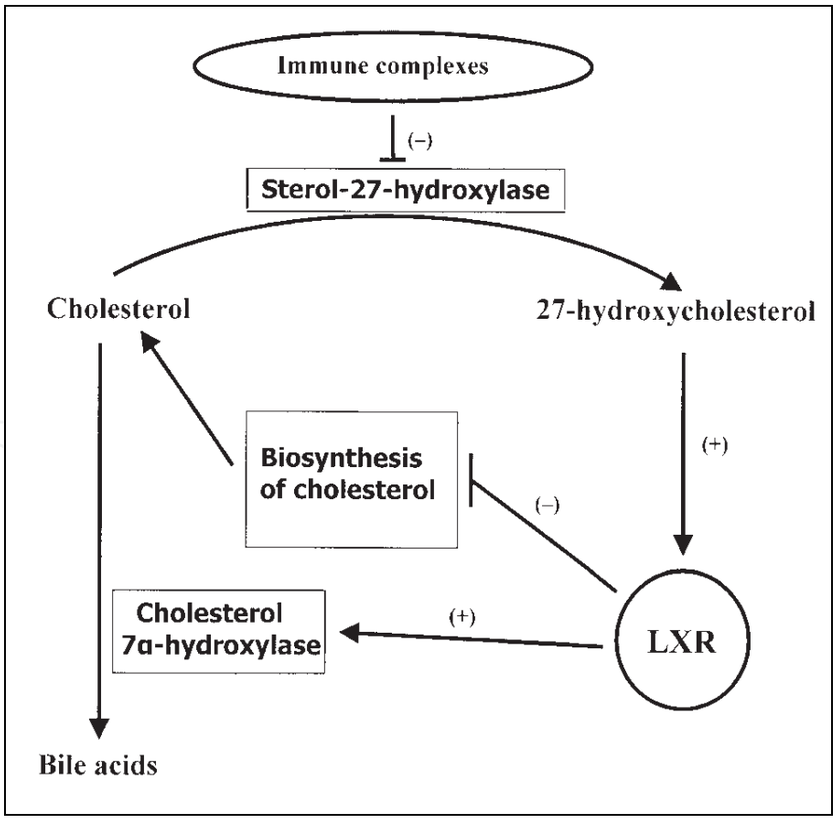


Fig. 11. A schematic representation of possible impact of immune complexes on the biosynthesis and catabolism of cholesterol

Described in this paper (see Table 5) increase of TNFα in the serum of *lupus* mice emerging simultaneously with the appearance of proteinuria and hypercholesterolemia, also can be attributed to decreased production of 27-hydroxycholesterol since oxysterols (via LXR) inhibit an expression and synthesis of proinflammatory cytokines (Dushkin et al., 1998; Hong et al., 2011). These currently available indirect evidences are in good agreement with the foregoing hypothesis, however its proof requires further experimental investigations.

2.2.7 Sex differences of autoimmune glomerulonephritis formation in the experimental model

As it's known there is a pronounced sexual dimorphism in the incidence of many human autoimmune pathologies, particularly systemic lupus erythematosus (Whitacre, 2001). It has been shown that the induction of chronic GVHD in the semiallogeneic system DBA/2→(C57Bl/10xDBA/2)F1 causes the formation of autoimmune pathology only in female recipients for up to 6 weeks (Van Griensven et al., 1997).

Parameter	Females		Males	
	control	*lupus*	control	*lupus*
renal cortex				
Tubules	90.2 (88-91)	66.3*#(50-81)	90.8 (89-93)	88.1# (79-96)
Glomeruli	3.4 (3-5)	1.5* (1-3)	3.9 (3-5)	2.0* (1-4)
Blood vessels	5.9 (5-7)	2.1*# (1-3)	5.3 (3-7)	3.4*# (2-5)
Leukocyte infiltration	0.2 (0-2)	13.2*# (5-19)	0	0#
Cylinders	0	7.4* (2-15)	0	3.6* (0-9)
Cysts and cavities with liquid	0	9.5* (3-21)	0	2.9* (0-7)
renal medulla				
Tubules and ducts	95.8 (95-96)	94.9 (93-97)	97.5 (97-99)	97.3 (95-99)
Blood vessels	4.0 (3-5)	1.3*# (1-2)	2.5 (1-4)	2.2# (1-4)
Cylinders	0	3.8*# (3-5)	0	0.5*# (0-1)

(M, (min-max); * - $p < 0.05$ between control and experimental group; # - $p < 0.05$ between experimental groups

Table 6. The relative area of the structures on the cut renal cortex and renal medulla (% of section area)

In case of DBA/2→(C57BL/6xDBA/2)F1 model it has been observed that induction of GVHD using female donor and host mice causes more severe glomerulonephritis than one using male donor and host. This is not due to differences in splenic homing, alloreactive precursor frequency, initial proliferation rates, or apoptotic rates but rather to sustained high proliferative activity at early stage of GVHR. Crossover studies (female donor and

male host; male donor and female host) has revealed that this effect is depended on the host sex (Lang et al., 2003). In our experiments chronic GVHD induced by transfer of female donor cells leads to the development of glomerulonephritis in recipients of both sexes by the end of 3 months. Kidney pathological picture in male recipients is characterized by less pronounced glomerular and tubular lesions, the absence of leukocyte infiltration and vessel walls damage compared with females littermates (Table 6) (Kudaeva et al., 2009). Determination of the testosterone level in the peripheral blood of female *lupus* mice has shown an increase of its concentration (6.1 nM compared with 4.8 nM in intact females of the same age, $p < 0.05$). It may be explained by the compensatory response to kidney damage, taking into account renotropic effect of testosterone. However testosterone level in female *nonlupus* recipients is also increased (7.7 nM, $p < 0.05$).

Currently great attention is paid to sex hormones as regulators of immune responses. Higher incidence of autoimmune pathologies in women, its changing during pregnancy, sex differences of immune response, the influence of sex hormones on Th1/Th2 balance identify the role of sex hormones, mainly estrogen, progesterone and testosterone, as mediators of sexual dimorphism in the immune system (Erlandsson et al., 2003; Soldan et al., 2003; Cutolo et al., 2004; Matejuk et al., 2004). Less pronounced renal damage in males and increase of testosterone level in female recipients suggest testosterone as a factor of regulation, suppressed autoimmune processes during chronic GVHD.

2.3 Modulation by Th1/Th2 balance shifting

Currently, there is evidence of the possibility of Th1/Th2 balance changing through a variety of factors under the immunopathological situations, in particular, under the development of allergic diseases (Kato et al., 1999; Raz & Spiegelberg, 1999; Tipping & Kitching, 2005). Since a formation of autoimmune glomerulonephritis induced by chronic GVHR is a Th2-dependent process whereas a development of chronic GVHR without a kidney damage is a Th1-dependent one it has been studied the possibility to change the direction of reaction by agents shifting Th1/Th2 ratio towards Th1 or Th2. Drugs have been administered during the induction of the reaction (the first and second week of GVHR). Results have assessed by the change in the proportion of *lupus* recipients at the end of the experiment (within 3 months after the transfer semiallogeneic cells).

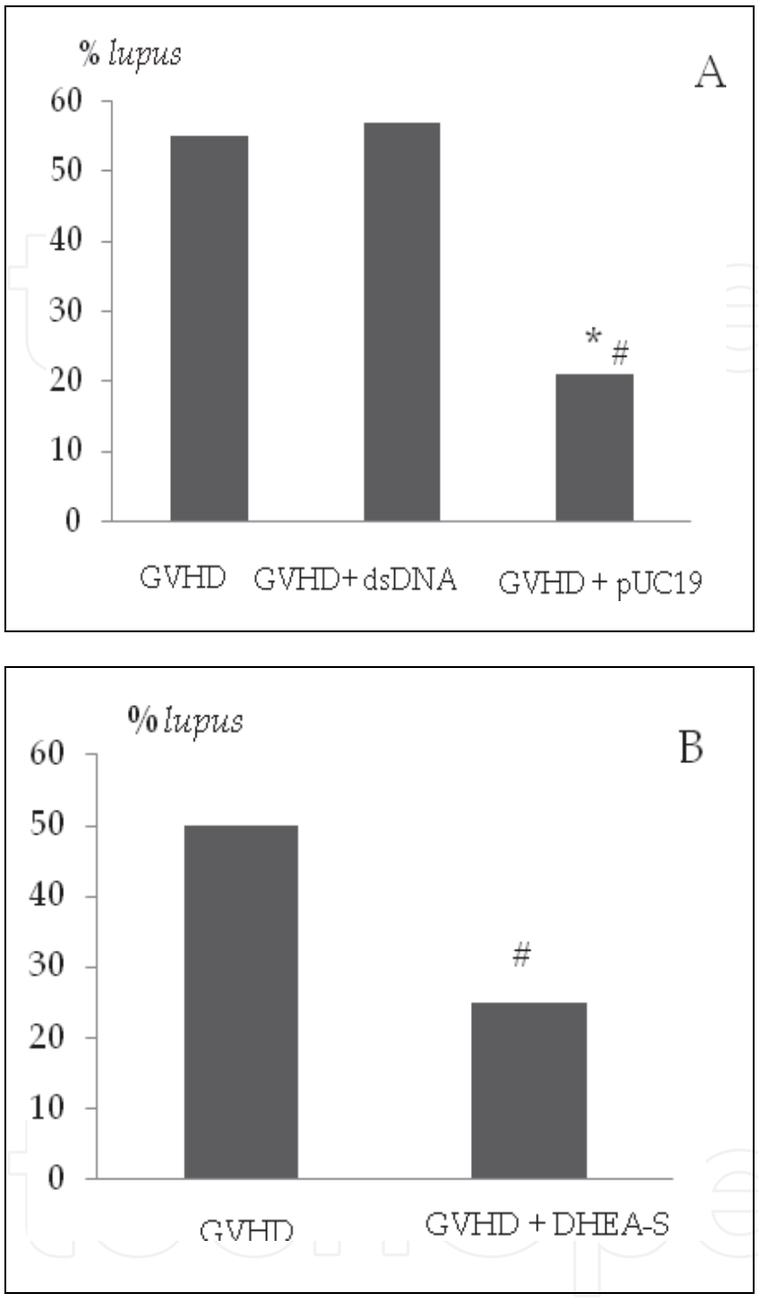
2.3.1 Shifting Th1/Th2 ratio towards Th1

DNA with immunostimulating properties (pUC19 plasmid DNA) and hormone dehydroepiandrosterone (in its transport form – dehydroepiandrosterone sulfate) are used as agents stimulating Th1 subpopulation.

It has been shown that injection of bacterial DNA containing nonmethylated CpG-plots stimulates production of Th1 cells activating cytokines: TNFα, IL-1, IL-12, IFNγ (Klinman et al., 1996; Carson & Raz, 1997; Krieg, 1999). pUC19 plasmid DNA is injected intravenously twice in dose 5 mg/kg. Calf thymus DNA in the same dose and scheme is used as a control.

Dehydroepiandrosterone sulfate is taken as Th1 activator (Stam et al., 1993; Rook et al., 1994; Sudo et al., 2001). Dehydroepiandrosterone sulfate restores production of Th1-dependent cytokines by old female mice (Araghi-Niknam et al., 1997). Dehydroepiandrosterone sulfate (Aldrich) has been injected subcutaneously 4 times in dose 37.5 mg/kg.

Results are shown in Figure 12. Both pUC19 plasmid DNA and dehydroepiandrosterone sulfate decrease the proportion of *lupus* recipients directing the reaction to Th1-dependent *nonlupus* variant (Vlasov et al., 2002; Tkachev et al., 2009).



* - $p < 0.05$ compared to GVHD; # - $p < 0.05$ compared to GVHD+dsDNA)

Fig. 12. Frequency of *lupus* mice among the recipients upon the effect of pUC19 plasmid DNA (A) and DHEA-S (B)

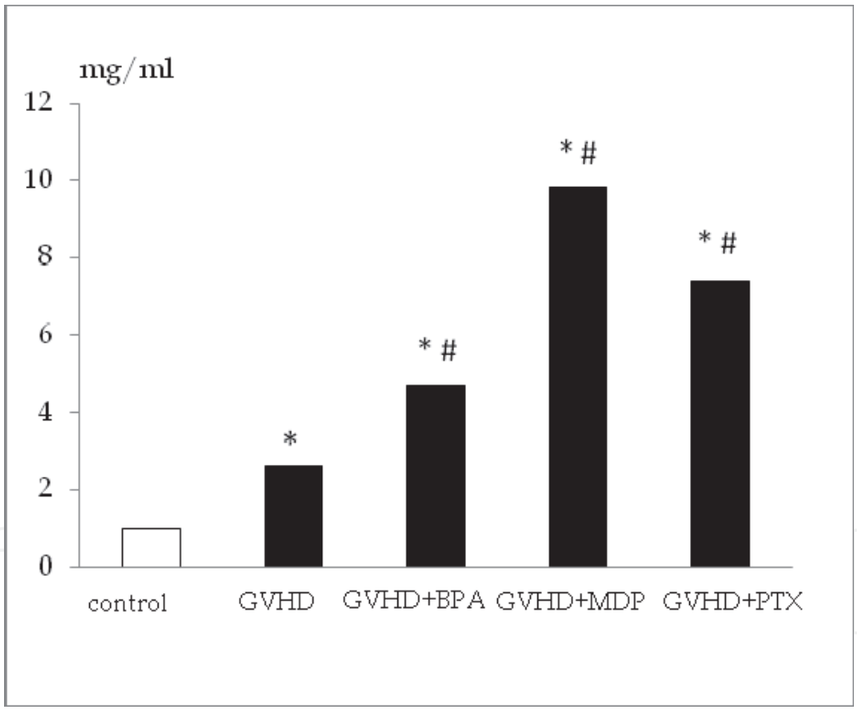
2.3.2 Shifting Th1/Th2 ratio towards Th2

It has been studied the possibility of modifying the course of reaction towards Th2-dependent processes also (Kudaeva et al., 2005b). Compounds with different mechanisms of action shifting the Th1/Th2 ratio towards Th2 cells have been used as immunomodulators: muramyl dipeptide, bisphenol A, and pentoxifylline. Muramyl dipeptide, a bacterial cell

wall derivative characterized by adjuvant effect, causes polyclonal activation of B-cells, and potentiates the stimulatory effect of IL-4 on activated B-lymphocytes (Souvannavong et al., 1990). Muramyl dipeptide (ICN) has been injected intraperitoneally in a dose of 1.0 mg/kg twice ten days apart. Bisphenol A widely used in the industrial manufacture of plastics binds to estrogen receptors despite structural differences from the hormone. It decreases production of IFNγ and synthesis of IgG2a (Sawai et al., 2003). Bisphenol A (ICN) has been given intraperitoneally in a daily dose of 2.5 μg/kg for 2 weeks. Pentoxifylline (a drug improving microcirculation and blood rheology) inhibits production of proinflammatory cytokines including IFNγ and suppresses the development of Th1-dependent experimental allergic encephalomyelitis in mice (Okuda & Sakoda, 1996). Pentoxifylline (Aventis Pharma Ltd.) has been given per os in a daily dose of 50 mg/kg for 1 week.

All these drugs cause an increased protein concentration in the urine of *lupus* recipients (Fig. 13) that strictly correlates with the severity of kidney damage (Kolesnikova et al., 1991). Moreover these drugs increase the incidence of lupus-like glomerulonephritis among recipients (Kudaeva et al., 2005b). Hence they deteriorate a course of a disease.

So, in this experimental model the change of the Th1/Th2 balance by introduction of immunomodulating drugs causes the amelioration or the progression of kidney damage.



* - p < 0.05 compared with control; # - p < 0.05 compared with GVHD; BPA - bisphenol A; MDP – muramyl dipeptide; PTX - pentoxifylline

Fig. 13. Protein concentration in urine of recipients

2.4 Correction of glomerulonephritis

In addition to studying the pathogenesis of autoimmune glomerulonephritis, it has been also investigated the possibility of correcting fully developed disease in this experimental model (Kudaeva et al., 2010a).

Lupus recipients have been lethally irradiated and then injected of bone marrow cells from intact syngeneic donors into a vein. Monitoring of follow-up processes have been included regular determination of the protein concentration in the urine. It has been found that such treatment of *lupus* recipients leads to a gradual decrease in the protein concentration in urine, the level of which is not differ from control values at the end of the experiment (Fig. 14). This result can be regarded as evidence of the positive effect of the therapy.

2.4.1 Immune parameters

At the end of the experiment it has been studied kidney morphology and measured body, thymus and spleen weight, cell number and the levels of total IgG and IgG-antibodies to DNA in peripheral blood.

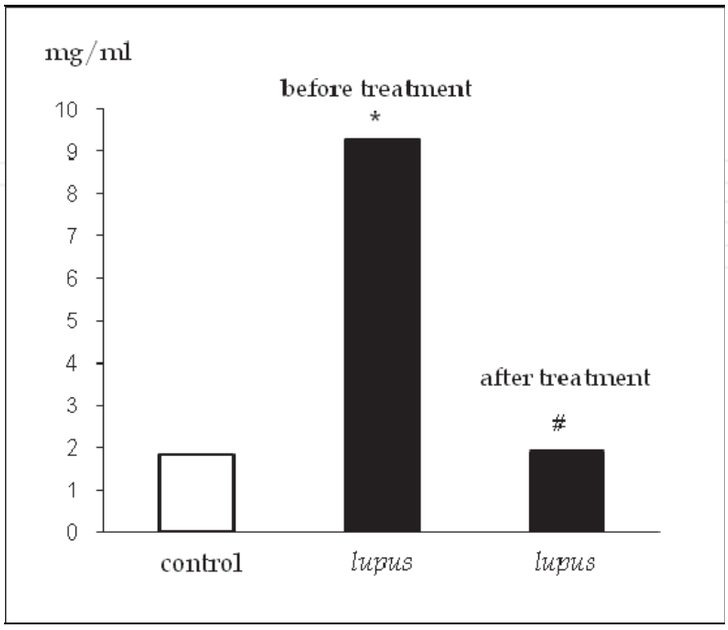
Mice with chronic GVHD are characterized by severe splenomegaly and polyclonal activation of B cells, leading to high levels of IgG in peripheral blood and the appearance of antibodies to components of its own tissues (Via & Shearer, 1988; Morris et al., 1990). After treatment spleen cells number and the concentration of IgG in peripheral blood of *lupus* recipients are not differ from the appropriate values of control (intact animals lethally irradiated and then injected of bone marrow cells from syngeneic donors). Correction of clinical manifestations of glomerulonephritis has been also accompanied by the disappearance of IgG antibodies to DNA from peripheral blood (Fig. 15).

It has not been significant difference in thymus weight between *lupus* mice before the treatment and control intact animals of the same sex and age. After the treatment its value in *lupus* recipients has diminished but has been not differ from irradiated and restored control. It may be due to slowing thymus recovery in mice of such age.

2.4.2 Kidney morphology

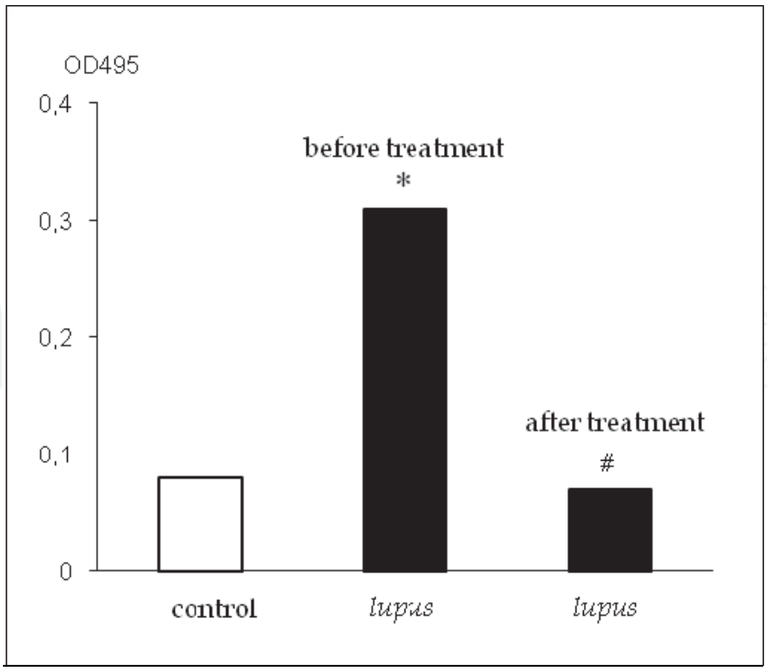
The results of morphological study of kidneys are presented in Tables 7-9. Formation of glomerulonephritis in *lupus* mice has been accompanied by development of inflammatory reaction with leukocyte infiltration, microcirculation change (an impairment of the permeability, a blockade of the venous capillaries) and lymphostasis in the renal parenchyma. All the pathological changes of the kidneys in *lupus* recipients indicate the active acute glomerulonephritis lasting for a long time (a different cell composition of leukocyte infiltrates, a large number of cylinders in the tubules and destructive changes in the glomeruli). After lethal irradiation and injection of syngeneic bone marrow cells it has been observed a fall in edema, in a severity of inflammation, in a leukocyte infiltration. In addition, a sharp decrease in the number of plasma cells in the leukocyte infiltrates, a large number of those present in *lupus* mice has been observed after therapy. At the end of the experiment number of plasma cells has been not differ from intact control values. Individual recipients have had various intensity of these changes. It has been no reverse development of pathological changes of glomeruli except of the reduction of leukocyte infiltration and edema. Restoration of structures of impaired glomeruli has been no observed. The latter is in agreement with the observation that regeneration of mammals kidney structure is demonstrated for renal tubular epithelium only (Hishikawa & Fujita, 2006; Poulsom et al., 2006; Bi et al., 2007). Another results have been obtained in a model of autosomally recessive Alport syndrome. Mice that lack the 3 chain of collagen IV fail to synthesize normal glomerular basement membrane and develop progressive glomerular damage leading to renal failure; bone marrow transplantation can rectify this podocyte

defect but the mechanisms underlying repopulation of glomerular podocytes by bone marrow-derived cells are not yet clear (Prodromidi et al., 2006).



* - $p < 0.05$ between control and experimental group, # - $p < 0.05$ between experimental groups

Fig. 14. Protein content in urine of recipients



* - $p < 0.05$ between control and experimental group; # - $p < 0.05$ between experimental groups

Fig. 15. The level of antibodies to dsDNA in peripheral blood of *lupus* recipients

Parameter	groups of animals *			
	1	2	3	4
Tubules	90.2[3,4**] (88-92)	88.9[4] (82-94)	66.3[1,4] (50-81)	78.5[1,2,3] (61-89)
Glomeruli	3.4[3,4] (3-5)	3.7[4] (3-5)	1.5[1] (1-3)	1.4[1,2] (0-3)
Blood vessels	5.9[2,3,4] (5-7)	3.7[1,4] (3-5)	2.1[1,4] (1-3)	4.9[1,2,3] (3-7)
Connective tissue	0	0	0	0
Leukocyte infiltration	0.2[2,3,4] (0-2)	1.9[1,4] (0-5)	13.2[1] (5-21)	9.8[1, 2] (6-14)
Cylinders	0[3,4]	0[4]	7.4[1,4] (3-15)	1.1[1,2,3] (0-3)
Cysts and cavities with liquid	0[2,3,4]	1.8[1] (0-5)	9.5[1,4] (3-21)	3.6[1,3] (0-18)
Hemorrhage	0.3 (0-10)	0	0	0.7 (0-5)

M, (min-max); * the groups of animals: 1 – control, intact mouse; 2 – the control, irradiation and transfer of bone marrow cells; 3 – the mouse with chronic GVHD, *lupus*; 4 – the mouse with chronic GVHD, *lupus,* irradiation and transfer of bone marrow cells; * [1, 2, 3, 4]– the groups that have significant differences among themselves

Table 7. The relative area of the structures on the cut renal cortex (% of section area)

Parameter	groups of animals*			
	1	2	3	4
Tubules and ducts	95.8[2,4**] (95-97)	96.6[1] (96-97)	94.9[4] (93-97)	97.1[1,3] (96-98)
Blood vessels	4.0[2,3,4] (3-4)	3.4[1,4] (3-4)	1.3[1,4] (1-2)	2.7[1,2,3] (2-4)
Connective tissue	0	0	0	0
Leukocyte infiltration	0	0	0	0
Cylinders	0[3]	0	3.8[1, 4] (2-5)	0.2[3] (0-1)
Cysts and cavities with liquid	0	0	0	0
Hemorrhage	0	0	0	0

M, (min-max); * the groups of animals as in table 7; * [1, 2, 3, 4]– the groups that have significant differences among themselves

Table 8. The relative area of the structures on the cut renal medulla (% of section area)

		groups of animals *			
		1	2	3	4
Number (N) of renal infiltrates (%)		10	60	100	100
Area cut infiltration	A_A****	0.2[3,4]** (0-2)	1.9[4] (0-5)	13.2[1] (6-18)	9.8[1, 2] (6-14)
	A*****	7500[2,3,4]	13500[1] (6875-26250)	37625[1,4] (26875-51875)	19375[1,3] (6250-42500)
Numerical density leukocytes (N_A***)		19.0	28.0 (16-37)	28.2 (19-40)	30.4 (21-37)
Neutrophils	%	0	0.8[4] (0-20)	2.3 (1-3)	2.1[2] (0-5)
	N_A	0	0.239[4] (0-0.68)	0.66 (0.24-1.14)	0.611[2] (0-1.11)
Monocytes	%	3	4.4 (2-7)	4.1 (3-5)	3.1 (1-4)
	N_A	0.57	1.18 (0.57-1.92)	1.17 (0.57-1.9)	0.931 (0.63-1.36)
Macrophages	%	48.0	22.4 (9-41)	24.8 (15-35)	23.7 (9-42)
	N_A	9.12	5.65 (2.43-7.68)	7.03 (3.15-13.3)	7.39 (2.1-14.28)
Fibroblasts and fibrocytes	%	18	8 (0-34)	1.2[4] (0-3)	9.6[3] (0-34)
	N_A	3.42	2.51 (0-10.2)	0.306[4] (0-0.96)	3.24[3] (0-12.58)
Plasma cells	%	0	10 (0-42)	17.7[4] (8-33)	2.1[3] (0-6)
	N_A	0	2.63 (0-8.96)	5.35[4] (1.9-13.2)	0.66[3] (0-1.92)

M, (min-max); * the groups of animals as in table 7; ** [1, 2, 3, 4]– the groups that have significant differences among themselves;
***N_A - numerical density of cells per 10^3 μm²;
****A_A - relative area of infiltration at the cut renal cortex (% of section area);
***** A - area of leukocyte infiltration (μm²).

Table 9. Characteristics of leukocyte infiltration in renal cortex

The data allow to conclude that induced by chronic GVHD immune complex glomerulonephritis of autoimmune genesis is maintained in the recipients by prolonged activity of immune cells. This inference is supported by data that the alloreactive donor T cells maintaining hyperplasia of host B lymphocytes with production of lupus-like antibodies persist in GVHD F1 mice for a long time after the induction of chronic GVHR (Rozendaal et al., 1990). Lethal irradiation interrupts the autoimmune process confirmed by disappearance of antibodies to DNA in peripheral blood and plasma cells in the kidney leukocyte infiltrates and consequently reduces the severity of kidney damage and leads to disappearance of clinical manifestations of glomerulonephritis – proteinuria.

3. Conclusion

Epigenetic mechanisms are long-term but reversible changes of gene activity not connected with DNA nucleotide sequence. Now it isn't doubted that epigenetic mechanisms play the important role in determination of individual immune reactions. A purposeful integration of immune reactions with adaptive processes of whole organism is achieved by epigenetic regulation (Vercelli, 2004; Reiner, 2005; Wilson et al., 2005). Consequently, the character of immune reactions and their final effects are not defined by the animal genotype and parameters of antigenic action on an organism only but are determined by its «epigenetic component» taking during ontogenesis also. In such a manner individual living conditions form the current stable state of immune system modifying immune characteristics of individual predetermined by genotype. Accompanied by genetic heterogeneity of natural populations these variations of immune parameters, based on epigenetic mechanisms, provide the observed diversity of individual responses to antigenic stimuli and form the perceptivity to infections and different diseases in developing of which functional activity of immune cells plays an appreciable role.

Th1 and Th2 activation has been shown to be affected in antagonist manner by numerous regulatory factors including hormones, mediators, and other biologically active substances (Rook et al., 1994; Piccini et al., 1995; Elenkov et al., 2000; Elenkov, 2004). The dissimilar level of biologically active molecules in recipient's organism may cause predominantly stimulation of Th1- or Th2-cells and as a consequence directs the GVHD development for Th1- or Th2-dependent ways and initiates predominantly the development of *nonlupus* or *lupus* variants respectively.

Experimental animals are a genetic homogenous group; transplanted cells have been identical for all recipients; the animal keeping conditions and transplanting procedure have been constant and the same for all mice in our work. Nonetheless there are two different variants of GVHD in our experiments. It is undoubtedly that even when experimental animals have identical genotype, there is always the dispersion of results that is usually considered as methodic imperfection. It is quite possible that such dispersion is rather an adequate reflection of the really existing situation: in spite of initial genetic identity animals are taking some stable distinctive properties in response to environmental influences by epigenetic mechanisms during ontogenesis (Jaenisch & Bird, 2003; Anway et al., 2005; Horsthemke & Ludwig, 2005; Reiner, 2005; Wong et al., 2005).

Thus, in spite of the genetic, sexual and age uniformity of recipients, the same living conditions and the standard transfer procedure, the trend of the chronic GVH disease can proceed in the classical Th2- or early not described Th1-dependent pathways in the DBA/2→(C57Bl/6xDBA/2)F1 system that eventually causes the development of two

variants of immunopathology, only one of them results in the autoimmune disorder – lupus-like immune complex glomerulonephritis. This model of the immunopathology permits the study of lupus-like nephritis pathogenesis. Furthermore it allows to use of GVHD in the DBA/2→(C57Bl/6xDBA/2)F1 system for devise practicable drugs and regimens of treatment during all stages of disease.

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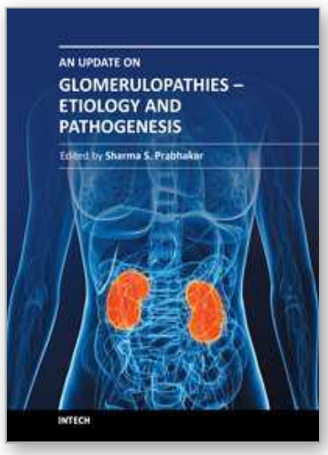

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The book has fourteen chapters which are grouped under different sections: Immune System and Glomerulonephritis, Animal Models of Glomerulonephritis, Cytokines and Signalling Pathways, Role of Cells and Organelles in Glomerulonephritis and Miscellaneous. While the purpose of this volume is to serve as an update on recent advances in the etio-pathogenesis of glomerulopathies, the book offers the current and broad based knowledge in the field to readers of all levels in the nephrology community.

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