УДК 616.34 – 097:616.4] – 092:599.324.2

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Expression of XBP1 in lymphocytes of small intestine rats under chronic social stress and modulation of intestinal microflora composition

the present study was conducted to investigate of the influence of chronic social stress and modulation of the composition of intestinal microflora on the distribution of Xbp1$^+$-lymphocytes in the gut-associated lymphoid tissue of ileum of the rats. Structure of population of Xbp1$^+$-cells has been studied by the analysis of serial histological sections using the method of indirect immunofluorescence with monoclonal antibodies to Xbp1 of rat. Chronic social stress development is accompanied with the reduction of total number of Xbp1$^+$-lymphocytes in lymphoid structures of ileum (31% -3 fold reduction, $p<0,05$), mostly expressed in lymphoid follicles, and changes the concentration of Xbp1 protein in immunopositive cells. Modulation of the composition of intestinal microflora by antibiotics and probiotics under chronic social stress results in the increase of total number of Xbp1$^+$ lymphocytes in gut-associated lymphoid tissue, the degree of it depends on the kind of stress. The discovered alterations of Xbp1 expression under stress may be one of the triggers for development of autoimmune and inflammatory bowel diseases. Thus, increased understanding of the molecular actions and transcriptional networks regulated by XBP1 in immune cells may aid in the development of potential therapeutics targeting immune disorders.
Key words: stress, gut-associated lymphoid tissue, transcription factor Xbp1, probiotics, antibiotics.

INTRODUCTION

Chronic social stress (CSS) is known to impact health, primarily via interactions among the nervous, endocrine, and immune systems that translate social experiences into physiological responses [1]. Specific stress-reactive pathways, including the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, facilitate intersystem communication via the release of glucocorticoids (GCs), catecholamines, and cytokines. It is widely accepted that stress affects the immune response, and chronic or repeated exposure to a stressor has been shown to be immunosuppressive. In large measure, suppression of immunity is due to the well-known anti-inflammatory effects of GC hormones. CSS, however, is not always immunosuppressive, particularly, if the stressor induces a state of functional GC resistance [2]. While the common view has been that stress suppresses immune system activity due to the suppressive effects of stress-induced GC hormones, there are now multiple studies demonstrating that stressor exposure can also enhance the immune response. Exposure to the stressor increases both innate and adaptive components of the immune system [1, 2]. Specific immunological changes that have been observed in mice following of CSS include: splenomegaly; elevated levels of circulating pro-inflammatory cytokines; enhanced expression of TLRs on bone marrow, blood, and splenic monocytes; and the development of functional GC resistance [3]. For example, the production of cytokines (e.g., TNF-α and IL-1β) is increased in LPS-stimulated splenic macrophages from mice exposed to the CSS [2, 3]. In addition, the ability of splenic macrophages to kill target Escherichia coli is significantly increased by exposure to the stressor [4]. Chronic social

stress is a risk factor for many affective and somatic disorders, including inflammatory bowel diseases (IBD), type 1 diabetes mellitus.

On the other hand, stress of different etiology may result in disorders of protein folding and induce the development of endoplasmic reticulum stress (ER stress). In eukaryotes, signals emanating from the ER induce a transcriptional program that enables cells to survive ER stress. This highly coordinated response, the Unfolded Protein Response (UPR), facilitates the folding, processing, export and degradation of proteins emanating from the ER during stressed conditions [5]. Three distinct UPR signaling pathways exist in mammalian cells that include ER transmembrane inositol-requiring enzyme-1α and β (IRE1α and β), protein kinase-like ER kinase (PERK), and activating transcription factor 6 (ATF6) [5]. Xbp1, first identified as a key regulator of major histocompatibility complex (MHC) class II gene expression in B cells, represents the most conserved signaling component of UPR and is critical for cell fate determination in response to ER stress. Collectively, reports on Xbp1 in immunity have revealed novel roles for this transcription factor in both innate and adaptive immune responses although interestingly, none are directly related to the function of MHC class II genes [5]. Thus, increased understanding of the molecular actions and transcriptional networks regulated by Xbp1 in immune cells may aid in the development of potential therapeutics targeting immune disorders.

A great number of works having been published on the role of disorders of Xbp1 production with epithelial cells of the intestine in the development of inflammatory and autoimmune diseases [6–9], we know nothing about the character of the given protein expression with gut-associated lymphoid tissue (GALT) [10] lymphocytes under CSS. That is why the aim of this work was to study the peculiarities of Xbp1 expression with lymphocytes of small intestine in Wistar rats under CSS and modulation of intestinal microflora composition with antibiotics and probiotics.

METHODS

Animals and experimental design

We studied 70 female Wistar rats (age 6 months) dividing them into seven experimental groups: control rats were orally given 0,5 ml of physiological salt solution intragastrically per three weeks (group 1); rats, whom CSS1 was modeled via 3 week social isolation and prolonged psychoemotional influence (PEI) implying permanent living of female in «aggressive environment» due to perforated partition in the cage with aggressive male confronting another planted male every day (group 2); rats, whom CSS2 was modeled via maintenance in overpopulated cage (20 rats in a cage) during 3 weeks with every day group change and the female under experiment was every day placed into a new balanced and overpopulated colony (group 3); rats with CSS1 and CSS2 whom the modulation of intestinal microflora composition was performed with daily intragastric administrations of aminoglycoside antibiotics Canamycine (Can) during 7 days beginning with the 3d week of modeling CSS in a dose of 15 mg/kg (group 4 and 5, respectively); rats with CSS1 and CSS2 whom modulation of intestinal microflora composition was performed via daily intragastric administrations of Lactobacterin (Lb, a mixture of live lyophilicaly dried lactobacteria of L. plantarum strain 8P-A3 and L. fermentum strain 90T-C4) during 3 weeks in a dose of 4×10^8CFU (group 6 and 7, respectively). The level of emotional-behavioral activity was established in the test «open field» accordingly the expression of experimental activity, the level of depression in animals was established in Porsolt test («forced swimming test», FST). The rats were removed from experiment with the method of decapitation under narcosis.

Immunofluorescence analysis

Population structure of $XBP1^+$-cells GALT was

studied basing on analysis of serial histological sections and findings of their morphometric and densitometric descriptions. To carry out this investigation on with rotary microtome MICROM HR-360 (Microm, Germany), 5-micron serial sections of iliac fixed according to Buen were performed, which were then deparaffined in xylol, rehydrated in decreasing concentrations of ethanol (100%, 96%, 70%), washed off in 0,1 M phosphate buffer

(pH = 7,4) and painted with primary rabbit monoclonal antibodies to Xbp1 rat (BioLegend) during 18 hours in a moist chamber in t = 4 C. After washing off the rest of primary antibodies in 0,1 M phosphate buffer, the sections were incubated for 60 minutes (T = 37 C) with secondary antibodies in solution 1:64. As secondary antibodies, goat's ones were used to full molecule IgG of rabbit, conjugated with FITC (SantaCruzBiotechnology, USA). The processed histological sections were studied with the help of computer program ImageJ (NIH, USA). Images obtained on the microscope PrimoStar (ZEISS, Germany) in ultraviolet spectrum of stimulation 390 nm (FITC) with the help of highly sensitive chamber AxioCam 5c (ZEISS, Germany) and program package for obtaining, archiving and preparation of the images for publication AxioVision 4.7.2 (ZEISS, Germany) were immediately introduced into computer. At the same time, the areas with statistically significant fluorescence distinctive for lymphoid tissues expressing Xbp1 were determined in automatic regime. The lymphoid follicles (Lf) and subepithelial zone of Peyer's patches (PP) and lymphocyte-filled villi (LFV) were studied.

Statistics

The results were statistically processed by means of software Statistica 6.0 (StatSoft, USA) using the Student's t-criterion. The results significantly differed in statistics at $P < 0,05$.

RESULTS AND DISCUSSION

The development of CSS was accompanied with the decrease of investigational activity of rats in test «open field» and increase of immobilization time as much as 50% comparatively the starting level in Porsolt test. It is known that rats under prolonged psycho-emotional impact (PEI) or social isolation developed pathological condition which was characterized with pronounced anxiety, decreasing of investigational and motor activity, as well as decreasing of communicative and pain sensitivity, disorders of estral cycle, sexual/social recognizing, and depression [11]. Besides, all the spectrum of characteristic stress-reaction changes that is the increase of suprarenal gland mass, adrenalin and noradrenalin levels, corticosterone (CS) release and others [11] was observed in those animals.

The study of serial sections of ileum in control Wistar rats first incubated with monoclonal antibodies to antigen Xbp1 showed that the total density of $Xbp1^+$ of lymphocytes is the highest in lymphoid follicles of Peyer's patches (PP Lf) – 120±5 on 1 mm^2, and this is caused by the prevalence of B-lymphocytes and plasmocytes having the most intensive expression of the given transcription factor in the given morphofunctional area, when the least one in LFV (Lymphocyte-filled villi) – 72±5 on 1 mm^2 (Fig.1). Among $Xbp1^+$ cells, $Xbp1^+$-small lymphocytes were predominant. There were from 60% (in LFV) to 68% (in PP Lf) of the total number of $Xbp1^+$ lymphocytes.

CSS development was accompanied with one-directed tendency on decreasing of total number of $Xbp1^+$ lymphocytes in lymphoid structures of ileum, mostly expressed in lymphoid follicles. Thus, total density of $Xbp1^+$-lymphocytes in LFV reduction was 31% (CSS1) – 35% (CSS2) ($P<0,05$), in subepithelial area of PP reduction was 47% (CSS2) – 58% (CSS1) ($P<0,05$), in PP Lf – 2,5 (CSS2) – 3 fold (CSS1) in comparison with control (Fig.1). The given reduction of the total number of $Xbp1^+$-cells occurred due to reduction of $Xbp1^+$-lymphocytes of all classes, the density of population and percentage of $Xbp\text{-}1^+$-lymphoblasts having being decreasing most intensively in every area. The measuring of fluorescence intensity of $Xbp1^+$-lymphocytes

expressing the concentration of Xbp1 protein in immunopositive cells showed the one-directed reliable reduction of this parameter in $Xbp1^+$-lymphoblasts, mostly expressed in CSS2, as well as the increase in $Xbp1^+$-medium lymphocytes and reduction in $Xbp1^+$-small lymphocytes in PP subepithelial zones in CSS1 (Fig.2).

The administrations of Can into experimental animals produced more pronounced influence on Xbp1 expression with GALT lymphocytes in CSS1. So, its oral intake had no influence on total density of $Xbp1^+$-lymphocytes in LFV, produced the increase of their number in PP subepithelial zones – 41% ($P<0,05$) only in CSS1 and contributed to intensive increase of their number in PP Lf – 66% ($P<0,05$) in CSS1 and 42% ($P<0,05$) in CSS2 (Fig. 1). At the same time, the study of Xbp1 protein concentration in immunopositive cells showed that the injections of Can were accompanied with different-directed changes of the given parameter in $Xbp1^+$-medium and small lymphocytes and didn't influence the level of its expression in $Xbp1^+$-lymphoblasts (Fig.2).

On the contrary, the administrations of Lb to stressed rats, unlike Can, had the most significant influence on Xbp1 expression with lymphocytes GALT in CSS2. Specifically, the total number of $Xbp1^+$-lymphocytes in animals subjected to CSS1 increased in only PP Lf (97%, $P<0,01$), while under influence of CSS2 their number increased in all studied morphofunctional zones - 70% in LFV ($P<0,05$), 63% ($P<0,05$) in PP subepithelial zone and 2 fold increase ($P<0,05$) in PP Lf (Fig. 1). Lb administrations produced a reliable increase of Xbp1 protein concentration in $Xbp1^+$-lymphoblasts (CSS2) and $Xbp1^+$-small lymphocytes (CSS1) and didn't influence the given index in $Xbp1^+$-medium lymphocytes (Fig. 2).

It is known that the alteration of Xbp1 expression may be a trigger of inflammatory and autoimmune diseases. The existence of an important link between cell-intrinsic ER stress and organ-specific inflammation has recently been reported within the intestines [7]. Specifically, conditional deletion of Xbp1 in the intestinal epithelium of mice was shown to result

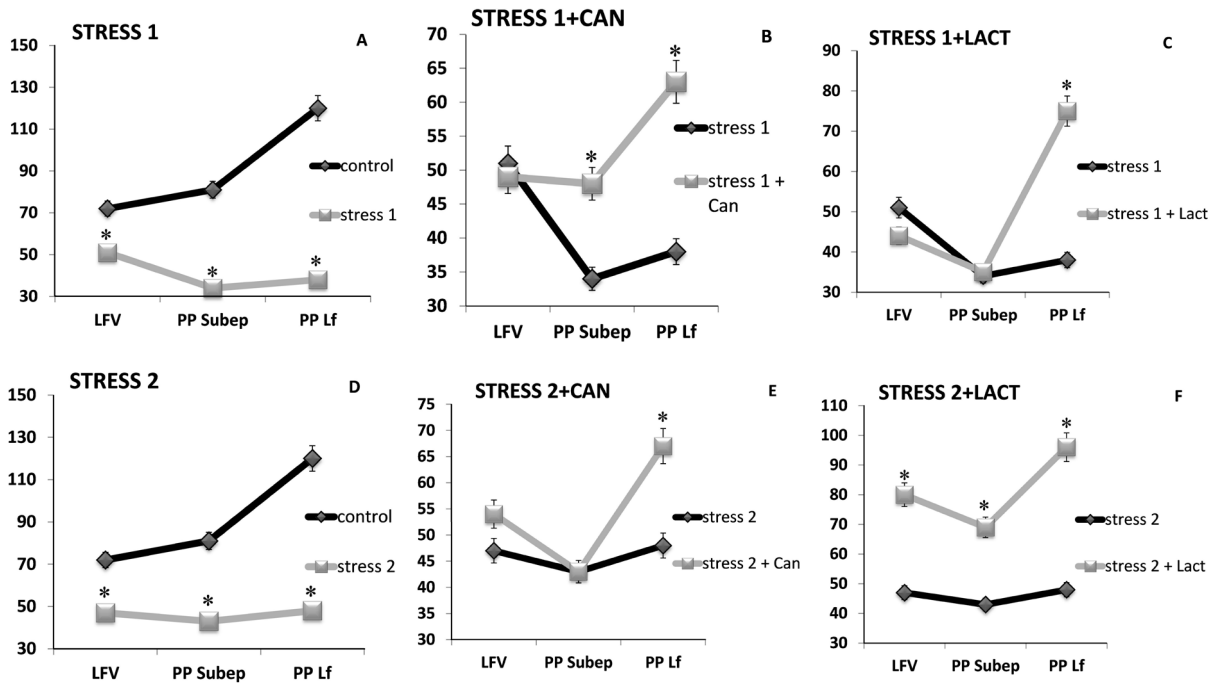

Fig. 1. The number of Xbp1-cells. Note: *$P<0,05$

in the spontaneous development of intestinal inflammation in the small intestine that presented with hallmarks of human IBD including crypt abscesses, leukocytic infiltration, and frank ulcerations [9]. Remarkably, even the deletion of one Xbp1 allele was sufficient to induce spontaneous enteritis in a significant portion of the animals [8, 9]. Moreover, hypomorphic Xbp1 with the loss of one allele also led to Paneth cell dysfunction and an increased susceptibility to DSS colitis and deletion of both alleles resulted in apoptotic cell death of Paneth cells [9]. Similar to rodents, studies in humans also suggest that ER stress can both be a primary cause of intestinal inflammation (e.g., as observed in Xbp1$^{-/-}$ mice) or a consequence of inflammation (e.g., as observed in IL-10$^{-/-}$ mice) [6, 9]. Patients with Crohn's disease and ulcerative colitis, two forms of IBD, exhibited decreased Xbp1s levels [6]. In addition, several genome-wide linkage studies hinted at an association between IBD and a region of the genome physically close to the Xbp1 gene and the IRE1β. Moreover, deep sequencing identified novel rare single nucleotide polymorphisms in Xbp1 that along with other environmental and genetic risk factors might confer susceptibility to IBD [8].

But in spite of absolute importance of alterations of Xbp1 expression with epithelial cells of the gut in the development of pathology, at present a whole series of works have shown the capacity of the given transcription factor to regulate the reactions of natural and adaptive immunity [12]. It was shown that TLR signaling activates the IRE1/Xbp1 axis and that this loop is crucial for host defense [13]. TLRs are well-conserved receptors that recognize pathogen-associated molecular patterns and danger signals. When macrophages were stimulated in vitro with agonists of TLR2 (Pam3CSK4) and TLR4 (LPS), the IRE1/Xbp1 pathway was activated independently of the other UPR branches and in the absence of ER stress [13]. Interestingly, treatment of macrophages with tunicamycin together with LPS caused an inhibition of ER stress triggered by tunicamycin [12]. To dissect the pathway, the authors looked for the events downstream of TLR that led to Xbp1 activation. They found that Xbp1 interacted with the promoter regions of genes IL6 and TNF, leading to sustained production of cytokines IL-6 and TNF-α. Xbp-1 dependence for in vitro and in vivo immunity against Francisella tularensis, a bacterium that activates TLR2, further confirmed the relevance of TLR-triggered Xbp1 activation [13]. The function of Xbp1 in innate immunity seemed to be highly conserved as similar observations were made in worms; Xbp1-deficient worms were hypersensitive to pathogen infection [14]. Therefore, Xbp1 plays a critical and protective role in both innate and adaptive immunity. This is not surprising given that the RNase domain of IRE1, both α and β, shares unique homology with RNase L, a critical component of the antiviral system that cleaves

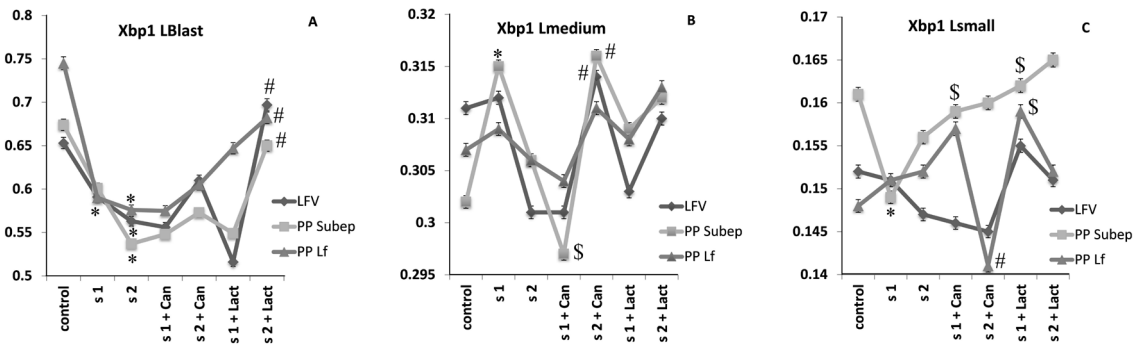

Fig. 2. Concentration of protein in Xbp1^{+}-lymphocytes. Note: *P<0,05 relative to the control, $^{\$}$P<0,05 relative to the stress 1, $^{\#}$P<0,05 relative to the stress 2

single-stranded RNA [12, 15]. The IRE1α-Xbp1 signaling pathway of UPR is also critical for the development and survival of another immune population, dendritic cells (DCs), particularly the plasmacytoid compartment (pDCs) [16]. Mice deficient of Xbp1 presented a smaller number of DCs, especially pDCs, and these cells secreted smaller amounts of IFN-α. Absence of Xbp1 also compromised the differentiation and survival of DCs and pDCs. Conversely, forced expression of Xbp1s enhanced DC development [16].

Besides, the discovered alterations of Xbp1 expression in stress may have a significant effect on the processes of differentiation of adaptive immune system cells. Xbp1 is required for plasma cell differentiation, but does not influence memory B cell commitment [17]. Xbp1-deficient B cells exhibited normal proliferation and activation, but expressed decreased levels of J chain, a component required for Ig assembly. Consequently, these animals were more susceptible to infections, but restoration of Xbp1s expression rescued Ig production. Xbp1-mediated ER expansion was required for adoption of a "professional secretory cell" phenotype characteristic of plasma cells [18, 19]. In addition, Xbp1s induced IL-6 expression in splenic B cells, a terminal differentiation factor. Thus, Xbp1 in professional secretory cells may have evolved additional functions allowing these cells to respond to "physiological" UPR. Hence, the timing and mechanism of UPR and Xbp1 activation during plasma cell differentiation remain an interesting and open question. Taking into consideration the importance antibodies play in protection of intestinal mucosa from pathogens, the possible consequences of discovered alterations of Xbp1 expression with lymphocytes of GALT become clear. Besides, these alterations may influence on the final production of autoantibodies by plasmocytes to cell antigens, and this explains a sharp increase in the frequency of autoimmune diseases in people subjected to the effect of social stress as well as to change the production of protective secretory IgA. The endoplasmic reticulum (ER) stress response is a possible critical event for the initial T-cell differentiation upon antigen recognition. Franco A. et al. studied the relationship between ER and Il-10 transcription in human Treg clones [20]. The induction of ER stress with a canonical stressor, thapsigargin, enhances Il-10 transcription. Salubrinal, a small molecule inhibitor of the eukaryotic translation initiation factor 2α (eIF2α) dephosphorylation, dramatically inhibits it [20]. Il-10 transcription is also enhanced by exogenous TNFα. These results disclose a role for ER stress in driving T cell plasticity.

CONCLUSION

1. GALT lymphocytes actively express Xbp1: the greatest number of $Xbp1^+$ cells is localized in Peyer´s patches lymphoid follicles, the least number – in LFV. $Xbp1^+$-small lymphocytes prevail among $Xbp1^+$-cells, they share from 60% (in LFV) to 68% (in PP Lf) of the total number of $Xbp1^+$ cells.

2. CSS development is accompanied with the reduction of total number of $Xbp1^+$-lymphocytes in lymphoid structures of ileum (31% – 3fold increase, $P<0,05$), mostly expressed in lymphoid follicles. It also changes the concentration of Xbp1 protein in immunopositive cells.

3. Modulation of the composition of intestinal microflora by antibiotics and probiotics under CSS results in the increase of total number of $Xbp1^+$ lymphocytes in GALT and depends on the kind of stress: Can administrations intensively increase their number in CSS1, and Lb administrations – in CSS2.

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ОСОБЕННОСТИ ЭКСПРЕССИИ XBP1 ЛИМФОЦИТАМИ ТОНКОЙ КИШКИ КРЫС В УСЛОВИЯХ ХРОНИЧЕСКОГО СОЦИАЛЬНОГО СТРЕССА И МОДУЛЯЦИИ СОСТАВА КИШЕЧНОЙ МИКРОФЛОРЫ

Исследовано влияние хронического социального стресса и модуляции состава кишечной микрофлоры на интенсивность экспрессии транскрипционного фактора Xbp1 иммунными клетками кишечно-ассоциированной лимфоидной ткани у крыс. Установлено, что развитие хронического

социального стресса сопровождается снижением общего количества Xbp1$^+$-лимфоцитов в лимфоидных структурах подвздошной кишки (на 31 % – в 3 раза, P<0,05), наиболее выраженном в лимфоидных фолликулах, а также изменяет концентрацию белка Xbp1 в иммунопозитивных клетках. Модуляция состава кишечной микрофлоры антибиотиками и пробиотиками в условиях хронического социального стресса приводит к увеличению общего числа Xbp1$^+$-лимфоцитов в кишечно-ассоциированной лимфоидной ткани, степень которого зависит от вида стресса. Обнаруженные изменения экспрессии Xbp1 в условиях стресса могут быть одним из триггеров развития аутоиммунных и воспалительных заболеваниях кишечника.
Ключевые слова: стресс, кишечно-ассоциированная лимфоидная ткань, транскрипционный фактор Xbp1, пробиотики, антибиотики.

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ОСОБЛИВОСТІ ЕКСПРЕСІЇ XBP1 ЛІМФОЦИТАМИ КЛУБОВОЇ КИШКИ ЩУРІВ В УМОВАХ ХРОНІЧНОГО СОЦІАЛЬНОГО СТРЕСУ І МОДУЛЯЦІЇ КИШКОВОЇ МІКРОФЛОРИ

Досліджено вплив хронічного соціального стресу та модуляції складу кишкової мікрофлори на інтенсивність експресії транскрипційного фактора Xbp1 імунними клітинами кишково-асоційованої лімфоїдної тканини у щурів. Встановлено, що розвиток хронічного соціального стресу супроводжується зниженням загальної кількості Xbp1$^+$-лімфоцитів у лімфоїдних структурах клубової кишки (на 31 % – у 3 рази, P<0,05), найбільш вираженим в лімфоїдних фолікулах, а також змінює концентрацію білка Xbp1 в імунопозитивних клітинах. Модуляція складу кишкової мікрофлори антибіотиками та пробіотиками в умовах хронічного соціального стресу призводить до збільшення загального числа Xbp1$^+$-лімфоцитів у кишково-асоційованій лімфоїдній тканині, ступінь якого залежить від виду стресу. Виявлені зміни експресії Xbp1 в умовах стресу можуть бути одним з тригерів розвитку автоімунних і запальних захворюваннях кишечника.
Ключові слова: стрес, кишково-асоційована лімфоїдна тканина, транскрипційний фактор XBP1, пробіотики, антибіотики.

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Received 06.08.2013