Вестник РУДН. Серия: МЕДИЦИНА
RUDN Journal of MEDICINE. ISSN 2313-0245 (Print). ISSN 2313-0261 (Online)
2021;25(3):181—195
http://journals.rudn.ru/medicine

ПУЛЬМОНОЛОГИЯ
PULMONOLOGY

DOI: 10.22363/2313-0245-2021-25-3-181-195

RESEARCH ARTICLE
НАУЧНАЯ СТАТЬЯ

Novel approaches to increase resistance to acute respiratory infections

Svetlana V. Guryanova[1, 2] ✉, Natalia A. Kudryashova[3], Anastasiya Kataeva[1], Bubusaira T. Orozbekova[4], Natalia V. Kolesnikova[5], Alexandr G. Chuchalin[6]

[1]Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry of Russian Academy of Sciences, *Moscow, Russian Federation*
[2]Peoples' Friendship University of Russia (RUDN University), *Moscow, Russian Federation*
[3]Institute of Biochemical Physics named after N.M. Emanuel of the Russian Academy of Sciences, *Moscow, Russian Federation*
[4]Kyrgyz State Academy of Physical Culture and Sports, *Bishkek, Kyrgyzstan*
[5]Kuban State Medical University, *Krasnodar, Russian Federation*
[6]Pirogov Russian National Research Medical University, *Moscow, Russian*
✉ svgur@mail.ru

Abstract. *Relevance*. Respiratory infections are the most common in the world. In order to prevent epidemics, there is a need to improve the strategies for organizing medical care and develop new approaches in order to increase the nonspecific resistance, mobilize innate immunity. *Objective*. The aim of this study was to investigate the effect of glucosaminylmuramyldipeptide (GMDP) on the level of expression of markers of differentiation and activation of functionally significant subpopulations of dendritic cells in peripheral blood mononuclear cells of healthy donors,the second aim was to assess the effectiveness of GMDP in the prevention of acute respiratory infections in an unfavorable epidemiological period of the COVID-19 pandemic. *Materials and Methods*. An open comparative study included 309 apparently healthy participants, aged 19—22 years. At the first stage of the study, 42 participants (22 female and 20 male) took the drug Licopid 1 mg for 10 days according to the instructions, 1 tablet 3 times a day in order to prevent acute respiratory infections. Peripheral blood sampling was performed before taking the drug (day 0) and the next day after the last dose of the drug (day 12). Evaluation of the expression of markers of differentiation and activation of dendritic cell subpopulations HLA-DR, CD11c, CD123, CD80, CD83, CCR7, CD3, CD14, CD20 was assessed by flow cytometry. At the same

time, mRNA was isolated from mononuclear cells of perfusion blood and, after reverse transcription, the level of gene expression was determined by RT PCR. At the next stage, the effectiveness of the prophylactic use of the drug Licopid in 267 students of the Institute of Physical Culture was assessed in order to prevent acute respiratory infections in an unfavorable epidemiological period; the observation period was 12 months. *Results and Discussion*. A study of the relative quantitative composition of DCs in the peripheral blood of healthy donors by flow cytometry revealed the possibility of an increase in their total number, as well as subpopulations of MDC and PDC under the influence of GMDP. There was a statistically significant increase in the receptors for the chemokine CCR7, which is responsible for the recruitment of DCs to the secondary lymphoid organs. Analysis of the levels of expression of genes *XCR1, CD11b*, and *CD103* showed a statistically significant effect of GMDP on an increase in their expression compared to the baseline level (before GMDP intake), with the mean value being higher in participants undergoing moderate exercise. It was found that the use of the drug Licopid 1mg for the purpose of preventing and reducing the seasonal incidence of acute respiratory infections at the stage of basic training of students of the Institute of Physical Culture contributed to a decrease in the incidence of acute respiratory infections within 12 months of observation after taking the drug. The number of episodes of acute respiratory infections decreased 3.7 times, while the group with 3 or more episodes of acute respiratory infections during the year, which constituted 14.5 % of participants, completely disappeared. The maximum efficiency of GMDP was observed in the track and field command, in which the number of participants who had no episodes of acute respiratory infections during the year increased by 7 times. *Conclusion*. Our data complement the modern understanding of the molecular mechanism of action of GMDP and substantiate the possibility of its experimental and clinical use in order to develop new strategies for organizing medical care in order to increase the nonspecific resistance of the organism.

Key words: innate immunity, glucosaminyl muramyl dipeptide, GMDP, mucosal immunity, prevention, acute respiratory infections, dendritic cells, CD80, CD83, CCR7, CD103, XCR1, CD11b

Author contributions. S.V. Guryanova and N.V. Kolesnikova — development of research design; S.V. Guryanova, A.A. Kataeva and N.A. Kudryashova — studies by flow cytometry and RT PCR; B.T. Orozbekova — clinical observation; S.V. Guryanova, N.V. Kolesnikova, B.T. Orozbekova — writing the manuscript; A.G. Chuchalin — editing the manuscript.

Conflict of interest statement. The authors declare no conflict of interest.

Received 09.06.2021. Accepted 30.07.2021.

For citation: Guryanova SV, Kudryashova NA, Kataeva AA, Orozbekova BT, Kolesnikova NV, Chuchalin AG. Novel approaches to increase resistance to acute respiratory infections. *RUDN Journal of Medicine*. 2021;25(3):181—195. doi: 10.22363/2313-0245-2021-25-3-181-195

Introduction

Respiratory diseases are the most common in the world and occupy a leading position in the number of medical visits [1]. The variability of microorganisms, including the evolution of viruses in natural ecosystems [2], the adaptation of bacteria to existing drugs, creates a constant threat of the emergence of new infections [3]. In order to prevent epidemics, there is a need to improve strategies for organizing medical care and the development of new drugs. The development of new vaccines and antibiotics takes a long time, and therefore the task of increasing the nonspecific resistance of the organism becomes urgent, including with the help of immunomodulators, which include ligands of innate immunity receptors [4].

Innate immunity receptors (TLR, NLR, RLR, etc.) are widely represented in cells of all organs and tissues, but their maximum amount is found in immunocompetent cells and epithelial cells located in mucous membranes and performing barrier functions [5]. The interaction of innate immunity receptors with their ligands normally leads to the initiation of a cascade of reactions aimed at the formation of an adequate immune response and elimination of the pathogen [6—8]. Ligands of innate immunity receptors are widely represented in medical practice as medicines and vaccine components [9—11], they are also widely used in experimental models for research in the field of immunity [12, 13], in particular, muramyl peptides. Muramylpeptides are part of the peptidoglycan of all known bacteria and some fungi. The sensors of muramyl peptides are NOD1 and NOD2 proteins of intracellular localization, which belong to the NLR family of innate immunity receptors. NOD1 recognize fragments of

peptidoglycan from Gram-negative bacteria, NOD2 specifically interact with fragments of peptidoglycan from Gram-negative and Gram-positive bacteria, as a result of which an anti-inflammatory response is initiated. One of the ligands of NOD2 receptor is glucosaminylmuramyl dipeptide (GMDP).

The drug based on GMDP — Licopid — has been used for more than twenty years in medicine to correct the immune status and secondary immunodeficiency states in various nosologies: in surgery — to prevent infectious complications and to correct cytopenias of various etiologies; as part of complex therapy is used in oncology.

The known mechanism of action through NOD2 receptors and its effectiveness in mobilizing an adequate immune response are the basis for the use of GMDP in various pathologies. The use of GMDP in the treatment of children with prolonged acute respiratory viral infections helped to get rid of bacterial complications and reduce relapses [14], in adults it helped to reduce the episodes of acute respiratory viral infections and normalized immunological parameters [15]. The effectiveness of GMDP in activating cellular immunity to fight viral and bacterial infections has been described in details, while the effect of GMDP on dendritic cells (DC) has not been studied. DCs play a leading role in the presentation of antigen to T cells and the formation of antigen-dependent immune responses; they play a central role in the coordination of innate and adaptive immunity, regulation and suppression of inflammatory processes. DC precursors, which are normally present in all tissues and organs, are activated under the action of PAMPs and DAMPs, and their phenotypic and functional characteristics change. The DC community is extremely diverse, several populations are distinguished based on their origin, susceptibility to various activation stimuli, phenotypic and functional characteristics. It is known that, under the action of activation stimuli, the phenotype of dendritic cell precursors changes; markers CCR7, XCR1, and CD103 are expressed on their surface, which makes it possible for them to move in tissues to form an adequate response to an activation stimulus. In addition, dendritic cells provide tolerance to harmless antigens and prevent excessive reactivity of immunocompetent cells [16]. Dendritic cells are a link between innate and adaptive immunity, coordinating the immune response to bacterial and viral infections, as well as to transformed cells [17].

The aim of this study was to study the effect of GMDP on the level of expression of markers of activation and differentiation of dendritic cells isolated from mononuclear cells of the peripheral blood of healthy donors, as well as to evaluate the effectiveness of the drug Licopid in the prevention of acute respiratory infections (ARI) in an unfavorable epidemiological period.

Materials and methods

An open comparative study involved 309 (42 and 267) participants aged 19—22 years. All study participants provided voluntary informed consent to participate in the study in accordance with the World Medical Association's Declaration of Helsinki (WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013) and the processing of personal data.

At the first stage of the study, 42 participants (22 female and 20 male, aged 19—22) took the drug Licopid 1 mg (AO Peptek, Russia) according to the instructions for 1 tablet 3 times a day in order to prevent acute viral infections of the respiratory tract for 10 days. Peripheral blood sampling was performed before taking the drug Licopid (day 0) and the next day after the last dose of the drug (day 12). Part of the peripheral blood was used for cytometric analysis, the other part was used for isolation of mononuclear cells followed by PCR.

To determine the quantitative ratio of myeloid dendritic cells (MDC) and plasmacytoid cells (PPC), as well as to determine the phenotype of their subpopulations, cytofluorometric analysis was performed using a NovoCyte Flow Cytometer (ACEA Biosciences Inc., USA). Due to the fact that there is no specific marker characteristic exclusively for DCs, a combination of several markers was used. Phenotyping was performed using markers HLA-DR, CD11c, CD123 against CD3, CD20, CD56, CD14; CD80, CD83, CCR7 (BD Biosciences, USA) were used as differentiation

markers. MDC populations were determined by HLA-DR + CD3- CD14- CD20- CD11c + CD123-, PDC was determined by markers HLA-DR + CD3- CD14- CD20- CD11c + CD123 + (BD Biosciences, USA).

Mononuclear cells (MNCs) were isolated using the Lympholyte CL5015 reagent (Cedarlane Lab. Ltd, Canada), layering venous blood diluted in physiological solution (Paneco, Russia) on the reagent in a ratio of 1: 3, followed by centrifugation at 4 °C. Isolation of mRNA was performed using TRIzol ™ Reagent (Thermo Fisher Scientific) according to the manufacturer's procedure. Reverse transcription was performed using the Mint cDNA synthesis kit (Evrogen, Russia). The level of gene expression was determined by RT PCR on a Bio-Rad CFX 96 thermal cycler. The constitutively expressed glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene was used as a reference gene (housekeeping gene). Primers used: *XCR1* 5'-CTCCTGTCTACTGCCTGTGTTG-3'(forward), 5'-TGACTGTTCGGTGTCTCTGTCT-3' (reverse); *CD103* (Integrin Subunit Alpha E) 5'-ACACAAGCCAAAGCCCTTCT-3 '(forward), 5'-CAGGCTCTTGACTCTGGGTG –3' (reverse); *GAPDH:* 5′-GGGTGTGAACCATGAGAAGT-3′ (forward), 5′-GACTGTGGTCATGAGTCCT-3 ′ (reverse). Gene expression was assessed by formula: R = 2- [ΔCt1-ΔCt2], where R is relative expression; Ct is the reaction saturation threshold (cycle threshold); 1- test gene, 2- GAPDH gene. When analyzing the results, we took into account the survey data, which reflected the number of ARIs per year, the level of physical activity, food preferences, in particular probiotics.

The next stage of the investigation was to assess the effectiveness of glucosaminylmuramyl dipeptide in the prevention of acute viral infections of the respiratory tract during an unfavorable epidemiological period. The investigation involved 267 students (130 female and 137 male) studying at the Kyrgyz State Academy of Physical Training and Sports (Bishkek, Kyrgyzstan) at the stage of basic training with moderate physical activity (2—3 hours a day). The participants were divided into two groups: participants in the control group of 124 people (66 female and 58 male) took GMDP 3 mg sublingually per day for 10 days. The drug Licopid was used according to the indications of the instructions for the prevention of acute respiratory infections. The participants in the comparison group of 143 people (71 female and 72 male) did not use GMDP. The distribution of participants by sport is shown in Table 1.

Table 1

Distribution of research participants (N = 267) by kind of sport

Type of sport	Sex	Quantity	Overall
Track and field	m	15	30
	f	15	
Boxing	m	29	39
	f	10	
Volleyball	m	27	57
	f	30	
Basketball	m	30	66
	f	36	
Fencing	m	19	36
	f	17	
Martial arts	m	17	39
	f	22	
All (n)	m	137	267
	f	130	
%	m	49	100
	f	51	

The distribution of participants into groups was carried out based on the number of ARI episodes in the previous period (1 year) in order to evenly distribute participants in each group who had 1—2 (28 %), 3 or more (14 %) ARI episodes per year. Time of the study: April 2020 — March 2021. During the observation period, the number of ARI episodes of participants was recorded, data was collected on the number of cases with a confirmed diagnosis of COVID-19 among study participants and their families.

Inclusion criteria were relative health, age 19—20 years, and willingness to participate in the study.

The exclusion criteria for all surveyed groups were smoking, chronic inflammatory and autoimmune diseases.

Statistical data processing was performed using the Mann — Whitney and Wilcoxon tests using the SPSS and Microsoft Excel software. Data are presented as mean and interquartile range. Values at $p < 0.05$ were considered statistically significant.

Results and discussion

The study of the relative amount and phenotypic characteristics of DCs in the peripheral blood of healthy participants by cytofluorimetry showed the DC content of 1.41 % (0.22—1.85 %). After a 10-day course of GMDP application, the amount of the total DC pool increased to 2.72 % (0.93—2.95 %). Along with this, significant changes in functionally significant populations of DC phenotypes were revealed in relation to the initial values before the intake of GMDP, the level of activated myeloid (MDC) and plasmacytoid (PDC) increased 1.9 times, while the ratio between these populations remained at the same level of –1.8 (Fig. 1).

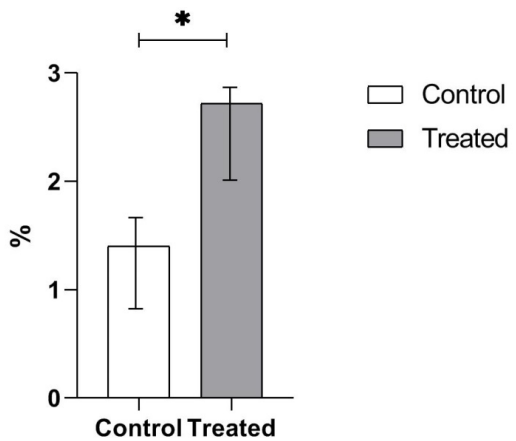

Fig. 1. The relative amount of myeloid and plasmacytoid dendritic cells in% of the total number of peripheral blood cells of healthy donors (N = 42) before taking GMDP and after a 10-day course

Note: * p <0.05

It is known that the ratio of MDC and PDC in healthy donors is 1.5—2 [19]. The level of deviation of the ratio of MDC and PDC from the level of healthy individuals indicates chronic inflammation, autoimmune processes, oncology and may be the cause of miscarriage [20—22]. In particular, in rheumatoid arthritis, the amount of MDC exceeds the amount of PDC by 10.2 times. This change in subtypes was caused by a 6-fold decrease in PDC compared to PDC healthy donors [23].

It is known that DCs are professional antigen-presenting cells with a complex and heterogeneous phenotype and functional plasticity [24]. DC precursors are formed in the bone marrow and through the blood enter the secondary lymphoid organs, the mucous epithelium of the barrier tissues (lungs, intestinal mucosa, etc.), and the skin. After interacting with the antigen, DCs differentiate and change their phenotype. The differentiation markers that appeared on their surface — chemotaxis receptors — determine the possibility of DC migration into secondary lymphoid organs for the presentation of antigen to T cells. The interaction of DCs with T cells is determined by surface receptors for DC activation, and the type of T-cell response is regulated by cross-presentation. Depending on the antigen, microenvironment and cross-presenting markers, different T-cell populations can be activated: Th1, Th2, Th17, Treg [17, 20]. In our study, maintaining the ratio of PDC and MDC at the same level under the influence of GMDP indicates the absence of chronic and autoimmune diseases in the study participants. MDC populations were determined by HLA-DR+ CD3-CD14 CD20 CD11c+CD123-, PDC was determined by markers HLA-DR+D3-CD14-CD20-CD11c+CD123+ (Fig. 2).

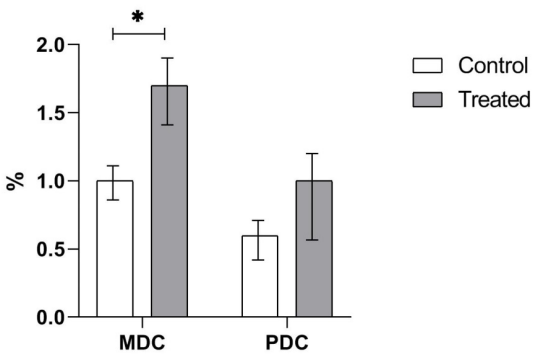

Fig. 2. The relative amount (%) of myeloid (MDC) and plasmacytoid dendritic cells (PDC) expressing the CD80 marker in the peripheral blood of healthy donors (N = 42) before taking GMDP and after a 10-day course

Note: MDC — myeloid DC; PDC — plasmacytoid DC; * p <0.05.

The number of DCs and optimal ratio of their subpopulations is a necessary condition for maintaining immune homeostasis. The degree of their maturity is

also of great importance. In various pathologies, defects were revealed at the stage of DC differentiation. For example, in rheumatoid arthritis and psoriatic arthritis, the absence of mature DC has been shown [19]. The main markers that determine DC maturity are CD80, CD83, and CCR7, which ensure DC migration to lymph nodes and interaction with T cells. The study showed that GMDP increases the expression of differentiation markers CD80, CD83 and CCR7 (Fig. 3—5). The ability to influence the degree of DC differentiation can serve as a justification for the previously discovered clinical efficacy of GMDP in psoriasis [11].

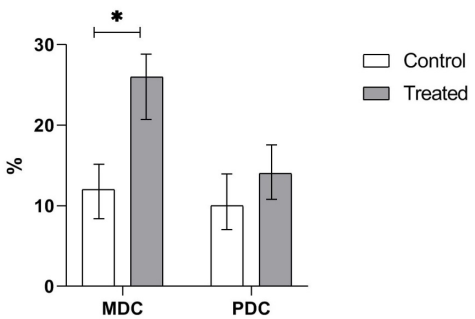

Fig. 3. The relative amount (%) of myeloid (MDC) and plasmacytoid dendritic cells (PDC) expressing the CD80 marker in the peripheral blood of healthy donors (N = 42) before taking GMDP and after a 10-day course

Note: MDC — myeloid DC; PDC — plasmacytoid DC; * p <0.05.

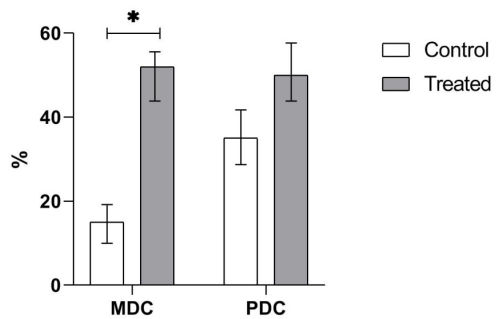

Fig. 4. The relative amount (%) of myeloid (MDC) and plasmacytoid dendritic cells (PDC) expressing the CD83 marker in the peripheral blood of healthy donors (N = 42) before taking GMDP and after a 10-day course

Note: MDC — myeloid DC; PDC — plasmacytoid DC; * p <0.05.

A significant increase in MDC and PDC with the CCR7 receptor was found compared to the baseline value, when comparing the percentage of dendritic cells expressing the CCR7 marker (CD197) before and after taking GMDP (Fig. 5).

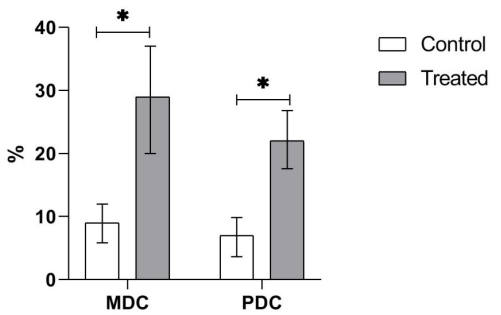

Fig. 5. The relative amount (%) of myeloid (MDC) and plasmacytoid dendritic cells (PDC) expressing the CCR7 marker in the peripheral blood of healthy donors (N = 42) before taking GMDP and after a 10-day course

Note: MDC — myeloid DC; PDC — plasmacytoid DC; * p <0.05.

CCR7 is a receptor for β-chemokines CCL19 and CCL21, it ensures the migration of DCs to afferent lymphatic vessels, homing of T cells to secondary lymphoid organs, and also coordinates the movement of B cells in lymph node follicles to the border of B and T cell regions for interaction with Th. In the external endothelial venules, CCL21 is expressed, interacting with which CCR7 directs immune cells to the secondary lymphoid organs. Thus, CCR7 is important for the formation of an antigen-specific immune response, ensuring the transport of DCs to secondary lymphoid organs [25—27]. In addition, constitutively expressed CCR7 provides self-tolerance [28] as well as tolerance to harmless antigens, including food and inhalation antigens [26, 27].

It was found that PDCs expressing CCR7 had a more significant increase when exposed to GMDP than MDCs (3,3 and 1.9 times, respectively). It should be noted that MDCs represent a heterogeneous population of DCs, which are divided into subpopulations DC1 and DC2, which differ phenotypically and functionally. Despite the fact that both subpopulations are able to capture antigen, migrate to secondary lymphoid organs

and present antigen to T cells, DC1 and DC2 differ in their ability to respond to different components of the microenvironment and activate T cells. The DC1 subpopulation expresses XCR1 and CD103 is capable of activating cytotoxic T cells and shifting the T helper balance towards Th1. DC2 express CD11b and shift the balance towards Th2, while both subpopulations are able to activate Th17 [29].

It is known that in normal peripheral blood DC1 and DC2 are present in insignificant amounts: 0.3—0.8 % DC1 and 0.02—0.06 % DC2, in contrast to other types of cells, such as MPC and Langerhans cells [29]. In this regard, changes in the expression of genes of activation markers under the influence of GMDP for these subpopulations were studied by PCR. For these purposes, the *XCR1*, *CD11b* and *CD103* genes were selected. The choice of these genes is due to the fact that infections of bacterial and viral etiology induce the appearance on the membrane of chemokine receptors (CCR7, XCR1), a receptor for the complement component (CD11b), and a receptor for E-cadherin — Integrin Subunit Alpha E (CD103). Expression of XCR1, CD11b and CD103 receptors indicates the activation of cells, promotes their migration into the follicles of the lymph nodes with subsequent movement into the zone of inflammation of the barrier tissues and indicates the implementation of the immune response.

XCR1 is a chemokine receptor that takes part in the cooperative interaction of T cells and DCs in response to an antigen in barrier tissues. In this study, the level of transcription of the XCR1 gene increased after the application of GMDP by 1.5 times (Fig. 6).

It is known that dendritic cells expressing the XCR1 receptor play a major role in maintaining immune homeostasis of the intestinal mucosa [30] and the mucous membranes of the upper respiratory tract [31]. The presence of XCR1 on DC ensures the formation of memory T cells and, as a consequence, a rapid immune response during secondary infection with viral and parasitic infections [32]. In addition, expression of XCR1 on DCs is also required for the maturation of regulatory T cells, for maintaining self-tolerance and suppressing inflammation [33]. One of the mechanisms for controlling excessive inflammation in the mucous membrane by dendritic cells with XCR1 is the production of transforming growth factor-β1 and retinoic acid from vitamin A, which causes the induction of peripheral T-regulatory cells and the synthesis of anti-inflammatory cytokines. [34]. The discovered ability of GMDP to increase the expression of XCR1 demonstrates the capacity of GMDP to control excessive inflammation in mucosal tissues.

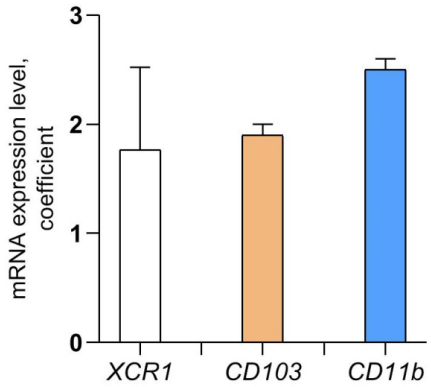

Fig. 6. Changes in mRNA transcription levels of genes XCR1, CD103 and CD11b in peripheral blood mononuclear cells of healthy donors (N=42) after a 10-day course of GMDP in relation to the initial level before usage GMDP; p <0.05.

CD103 — ITGAE (alpha E integrin subunit) is an E-cadherin receptor and mediates adhesion to epithelial cells. E-cadherin is one of the main molecules of Ca^{2+} -dependent cell-cell adhesion in epithelial tissues. CD103 is present on T cells and DCs for migration to the site of inflammation [35—37]. CD103+ DCs located in the lungs, intestines and skin, through cross-presentation, present a cytotoxic T cell-processed mechanism, providing protection against infection. CD103+ DCs influence the formation of regulatory T cells, limiting inflammatory responses and maintaining homeostasis [38]. The effect of GMDP on the expression of the CD103 gene is shown in (Fig. 6).

It should be noted that CD103 plays a key role in lung clearance from influenza virus [39] with cross-presentation protecting dendritic cells from moreover,

cross-presentation protects dendritic cells from infection with influenza virus [40]. The presence of CD103 + DC and CD103 + T cells is a predictor of a favorable outcome in oral cancer therapy [41]. The ability to enhance the expression of CD103, discovered in this study explains the positive clinical effects of GMDP in pulmonology [10, 14, 15].

Integrin alpha-M (CD11b) is a receptor for the C3b component of complement, recognizes fibrinogen and cell adhesion molecules present on the membranes of endothelial cells and leukocytes. The effect of GMDP on the increase in the expression of the *CD11b* gene is shown in (Fig. 6). It is known that *CD11b* participates in site-specific localization of DCs together with [34], constitutively supporting the maturation of Th17 [42]. CD11b+ DCs express proteins that provide contacts with epithelial cells in order to capture by dendrites, representatives of microorganisms of the intestinal lumen [43].

Dendritic cells represent a heterogeneous population of cells with a high level of plasticity. The appearance of various markers on their surface upon activation is finely regulated by inflammatory stimuli, and, which is important, triggers feedback mechanisms that stop and complete the process of inflammation. The study of the effect of GMDP on the expression of phenotypic markers of DC can supplement our understanding of the mechanisms of the implementation of the immune response upon activation of innate immunity receptors, manifested not only in the initiation of inflammatory stimuli, but also in their arrest, preventing excessive inflammation observed in experiment and clinical practice [44, 45].

An increase in the expression levels of differentiation markers via GMDP indicates its ability to regulate DC recruitment and the ability to influence the direction of the immune response.

It should be noted that when analyzing the results of gene expression under the influence of GMDP, the expression results were grouped according to the survey data, which reflected the number of ARIs per year, the level of physical activity, food preferences, and diet in order to identify significant factors. It turned out that gender, the number of ARIs per year and food preferences in this group were not significant, and the participants grouped according to these characteristics had the same values as the entire group. At the same time, the study participants (N = 9), experiencing moderate physical activity (2—3 hours per day), had median values in relation to the rest of the participants were higher (000 versus 000), which confirms the beneficial effect of moderate physical activity on stabilization and maintenance of the reactive ability of immunocompetent cells.

Thus, a statistically significant effect of GMDP on the expression of genes of DC activation markers XCR1, CD11b, and CD103 was observed in comparison with the initial state (before taking the drug Licopid) of healthy donors 19—20 years old, and the mean value was higher in participants experiencing moderate physical exercise.

The data obtained explain the clinical results with the use of GMDP for the prevention of acute respiratory diseases in 267 students of the Institute of Physical Culture, experiencing moderate physical activity (2—3 hours per day).

The use of the drug Licopid 1mg in order to prevent and reduce the seasonal incidence of acute respiratory infections at the stage of basic training of students of the Institute of Physical Culture contributed to a decrease in the incidence of acute respiratory infections within 12 months of observation after taking the drug. If, before taking the drug Licopid, 42.7 % of participants had a history of acute respiratory infections in the previous 12 months of observation, then after using the drug, this value dropped to 11.4 % (Table 2).

It should be noted that the use of GMDP completely disappeared the group with 3 or more episodes of acute respiratory infections during the year, which accounted for 14.5 % of participants. At the same time, in the comparison group, the number of ARIs during the observed period did not change significantly. Obviously, the number of ARI episodes after taking GMDP has decreased to a much greater extent, since the group that had 3 or more ARI episodes per year has completely disappeared. Analysis of the results of the GMDP effect by kind of sport showed that the greatest efficiency was observed in the student group track and field, in which

the number of participants who had no episodes of acute respiratory infections during the year increased by 7 times. In sports using general equipment (volleyball and basketball), the number of students of the Institute of Physical Culture, who have never been sick has increased by 50 % or more. In contact sports — boxing and martial arts — the use of GMDP also significantly contributed to a decrease in ARI episodes. At the same time, there was no statistically significant change in fencing, but the most favorable situation was observed in this kind of sport — 85 % of students specialized in this kind of sport, did not have acute respiratory infections during the year.

Table 2

The number of episodes of acute respiratory infections per year before and after taking GMDP

Type of sport	Before taking GMDP			After taking GMDP			Overall
	1—2 times per year	More than 3 times per year	Were not sick within a year	1 time per year	2 times per year	Were not sick within a year	
Track and field athletics	9	5	2	1	1	14	16
Boxing	7	2	9	1	1	16	18
Volleyball	6	4	14	2	0	22	24
Basketball	5	5	18	3	1	24	28
Fencing	2	1	16	0	2	17	19
Martial arts	6	1	12	1	1	17	19
All (n)	35	18	71	8	6	110	124
%	28.2	14.5	57.3	6.6	4.8	88.6	100

It is known that, with the exception of injuries, upper respiratory tract diseases are the most frequent manifestation of the disease in [46—48]. Although the frequency of ARI in athletes is comparable to the frequency in the general population, the timing differs from typical seasonal fluctuations, episodes appear more often in the pre-competition period and during the competition [49]. The unfavorable state of the upper respiratory tract has a negative impact on aerobic processes, muscle contraction and information processing ability [50—51]. The maximum number of episodes of acute respiratory infections in the group of athletes in comparison with athletes of other sports indicates the tension of mucosal immunity and a decrease in the adaptive capabilities of the organism. A 7-fold reduction in this group of ARI episodes when taking GMDP confirms its effectiveness in increasing the body's resistance to acute viral infections of the respiratory tract, previously established for children and adults [52].

The next stage of the study was to analyze the effect of GMDP on the body's resistance to acute viral infections of the respiratory tract in a difficult epidemiological situation against the background of an increase in the incidence of COVID-19.

During the entire observation period, cases of COVID-19 diseases were recorded in students of the Institute of Physical Culture and their family members of the main group (Table 3) and the comparison group (Table 4). All COVID-19 episodes in both groups were mild, moderate and severe, with no deaths.

Table 3

Students of the Institute of Physical Culture who have had contact with family members with a confirmed diagnosis of COVID-19 who have taken GMDP

Type of sport	Were in contact with someone diagnosed with COVID-19						Were not in contact with someone diagnosed with COVID-19			Overall		
	Mild course of the disease (were not hospitalized)			Traditional course of the disease (hospitalized)								
Track and field	7	m	4	3	m	1	6	m	4	16	m	9
		f	3		f	2		f	2		f	7
Boxing	9	m	8	2	m	2	7	m	3	18	m	13
		f	1		f	0		f	4		f	5
Volleyball	6	m	3	2	m	1	16	m	9	24	m	13
		f	3		f	1		f	7		f	11
Basketball	9	m	5	3	m	2	16	m	5	28	m	12
		f	4		f	1		f	11		f	16
Fencing	7	m	5	2	m	0	10	m	6	19	m	11
		f	2		f	2		f	4		f	8
Martial arts	9	m	5	1	m	0	9	m	3	19	m	8
		f	4		f	1		f	6		f	11
All (n)	47	m	30	13	m	6	64	m	30	124	m	66
		f	17		f	7		f	34		f	58
%	37.9			10.5			51.6			100		

In the group taking GMDP, 48.4 % of participants were in contact with a COVID-19 patient, while 98.4 % of participants did not have COVID-19.

Comparison of the episodes of the disease among the participants revealed that in the group taking GMDP, 2 people had a history of confirmed COVID-19, which is 1.6 %. In the comparison group, who did not take GMDP, this figure is 6 times higher — 9.8 % (14 people) (Fig. 7).

It should be noted that 2 study participants who took GMDP and had a history of confirmed COVID-19 had a mild coronavirus infection, unlike those in the group who did not receive GVDP: 4 out of 14 required medical attention.

Adverse reactions after the use of GMDP corresponded to those set out in the instructions, were mild and did not require discontinuation of the drug, 75.4 % of the participants did not experience adverse reactions.

Thus, the use of the drug Licopid contributed to a 3.7-fold decrease in the number of students of the Institute of Physical Culture who had ARI during the year, and the number of ARI episodes decreased to a much greater extent, since the group that had 3 or more ARI episodes per year completely disappeared. The use of GMDP contributed to an increase in nonspecific resistance and protection of 98.4 % of participants from COVID-19 during an unfavorable epidemiological period (April 2020 — March 2021). For the first time, the study covers a large group of participants with moderate physical activity, who used Licopid for prophylaxis.

Table 4

Students of the Institute of Physical Culture from the comparison group (age from 19—20 years old) who had contact with a patient with COVID-19.

Type of sport	Were in contact with someone diagnosed with COVID-19						Were not in contact with someone diagnosed with COVID-19			Overall		
	Mild course of the disease (were not hospitalized)			Traditional course of the disease (hospitalized)								
Track and field	8	m	3	2	m	1	4	m	2	14	m	6
		f	5		f	1		f	2		f	8
Boxing	12	m	11	4	m	2	5	m	3	21	m	16
		f	1		f	2		f	2		f	5
Volleyball	21	m	10	3	m	2	9	m	2	33	m	14
		f	11		f	1		f	7		f	19
Basketball	23	m	12	5	m	2	10	m	4	38	m	18
		f	11		f	3		f	6		f	20
Fencing	9	m	5	1	m	0	7	m	3	17	m	8
		f	4		f	1		f	4		f	9
Martial arts	10	m	6	1	m	0	9	m	3	20	m	9
		f	4		f	1		f	6		f	11
All (n)	83	m	47	16	m	7	44	m	17	143	m	71
		f	36		f	9		f	27		f	72
%	58.0			11.2			30.8			100		

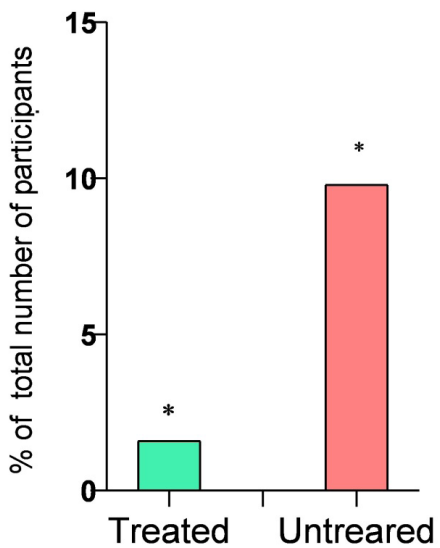

Fig. 7. Number of participants (%) in the study (N = 267, age 19—20 years) with a confirmed COVID-19 disease during 12 months of observation; * p <0.05.

This clinical observation is consistent with the previously obtained results of the positive effect of GMDP in the prevention of acute respiratory infections in children and adults [14, 15, 52].

The limitation of this study includes the narrow age range of the participants.

Our data reveal the molecular mechanism of GMDP action on functionally significant DC subpopulations and substantiate the clinical efficacy of GMDP use in the prevention of acute respiratory infections in 267 apparently healthy donors with moderate physical activity.

Conclusion

1. A new way of managing the recruitment of immune competent cells was discovered.
2. The possibility of a directed change in the phenotype of functionally significant subpopulations

of dendritic cells under the action of an agonist of NOD2 receptors of innate immunity was established.

3. Glucosaminylmuramyldipeptide (GMDP) promotes an increase in the amount of DCs, and significantly increases the expression of markers of differentiation and activation of DC.

4. Thus, new molecular mechanisms of GMDP action on DCs have been revealed and its clinical efficacy in the prevention of acute respiratory infections has been substantiated.

5. The experimental data explain the molecular mechanism of action of GMDP in the prevention of acute respiratory infections in people leading an active lifestyle, with moderate physical activity.

References/ Библиографический список

1. Troy NM, Bosco A. Respiratory viral infections and host responses; insights from genomics. *Respir Res*. 2016;17:156. DOI: 10.1186/s12931-016-0474-9

2. Chuchalin AG. COVID-19 and human security. *Terapevticheskii arkhiv*. 2021;93(3):253—254. DOI: 10.26442/00403660.2021.03.200717 (in Russian)

[*Чучалин АГ*. COVID-19 и безопасность человека. Терапевтический архив. 2021;93(3):253—254.]

3. Andersson DI, Balaban NQ, Baquero F, Courvalin P, Glaser P, Gophna U, Kishony R, Molin S, Tønjum T. Antibiotic resistance: turning evolutionary principles into clinical reality. *FEMS Microbiol Rev*. 2020;44(2):171—188. DOI: 10.1093/femsre/fuaa001

4. Khaitov RM. Immunomodulators: myths and reality. *Immunologiya*. 2020;41(2):101—106. DOI: 10.33029/ 0206-4952-2020-41-2-101-106 (in Russian)

[*Хаитов Р.М*. Иммуномодуляторы: мифы и реальность. Иммунология. 2020 № 41(2). С.101—106. DOI: 10.33029/ 0206-4952-2020- 41-2-101-106

5. Lavelle E, Murphy C, O'Neill L, Creagh EM. The role of TLRs, NLRs, and RLRs in mucosal innate immunity and homeostasis. *Mucosal Immunol*. 2010;3:17—28. DOI: 10.1038/mi.2009.124

6. Khaitov RM. Immunology: structure and function of immune system. *Textbook*. 2nd, renewed. M.: GEOTAR-Media, 2019. 328 p. (in Russian)

[*Хаитов Р.М*. Иммунология: структура и функции иммунной системы: учебное пособие. 2-е изд., перераб. М.: ГЭОТАР-Медиа, 2019. 328 с.]

7. Guryanova SV, Makarov EA, Meshcheryakova EA. Immunostimulating properties of GMDP and its analogues. *1st All-Union Immunological Congress (Sochi, July 15—17, 1989)*. Abstract Book. M: 1989;1:297. (in Russian)

[*Гурьянова С.В., Макаров Е.А., Мещерякова Е.А.* Иммуностимулирующие свойства ГМДП и его аналогов. I-ый Всесоюзный иммунологический съезд (Сочи, 15—17 июля 1989 г.). Тезисы докладов. М., 1989. Т. 1. С. 297.]

8. Guryanova S, Shvydchenko I, Kudryashova N. Bacterial agonist of innate immunity LPS regulates spontaneous and induced production of alfa defensins of human neutrophils in vitro. *Allergy: European Journal of Allergy and Clinical Immunology*. 2019;74(Suppl.106): 794. TP1556. DOI: 10.1111/all.13961

9. Benko S, Magyarics Z, Szabó A, Rajnavölgyi E. Dendritic cell subtypes as primary targets of vaccines: the emerging role and cross-talk of pattern recognition receptors. *Biol Chem*. 2008;389(5):469—85. DOI: 10.1515/bc.2008.054.

10. Guryanova SV, Khaitov RM. Strategies for Using Muramyl Peptides — Modulators of Innate Immunity of Bacterial Origin — in Medicine. *Frontiers in Immunology*. 2021;12:607178. DOI: 0.3389/fimmu.2021.607178

11. Guryanova S, Udzhukhu V and Kubylinsky A. Pathogenetic Therapy of Psoriasis by Muramyl Peptide. *Front. Immunol*. 2019;10:1275. DOI: 10.3389/fimmu.2019.01275

12. Xiao Q, Li X, Li Y, Wu Z, Xu C, Chen Z, He W. Biological drug and drug delivery-mediated immunotherapy. *Acta Pharm Sin B*. 2021;11(4):941—960. DOI: 10.1016/j.apsb.2020.12.018

13. Rechkina EA, Denisova GF, Masalova OV, Lideman LF, Denisov DA, Lesnova EI, Ataullakhanov RI, Gur'ianova SV, Kushch AA. Epitope mapping of antigenic determinants of hepatitis C virus proteins by phage display. *Mol Biol* (Mosk). 2006;40(2):357—68. PMID: 16637277

14. Ivanova V.V., Govorova L.V., Vershinina E.N. The effect of immunomodulatory therapy on the metabolic response of lymphocytes in ARVI patients against the background of herpes infection. *Childhood infections*. 2006;5(2):6—11. (in Russian)

[*Иванова В.В., Говорова Л.В., Вершинина Е.Н.* Влияние иммуномодулирующей терапии на метаболический ответ лимфоцитов у больных ОРВИ на фоне герпетического инфицирования. Детские инфекции. 2006. Т. 5. № 2. С. 6—11.]

15. Serkova N.A., Serkov I.L., Kulakov A.V. The use of a new domesticimmunocommodator Likopid to reduce seasonal incidence. *Immunologiya*. 2000;3: 62—63. (in Russian)

[*Серкова Н.А., Серков И.Л., Кулаков А.В.* Использование новогоотечественного иммуномодулятора Ликопида для снижения сезонной заболеваемости // Иммунология. 2000. № 3. С. 62—63.]

16. Hintzen G, Ohl L, del Rio ML, Rodriguez-Barbosa JI, Pabst O, Kocks JR. Induction of tolerance to innocuous inhaled antigen relies on a CCR7-dependent dendritic cell-mediated antigen transport to the bronchial lymph node. *J Immunol*. 2006;177:7346—54. DOI: 10.4049/jimmunol.177.10.7346

17. Granot T, Senda T, Carpenter DJ, Matsuoka N, Weiner J, Gordon CL, Miron M, Kumar BV, Griesemer A, Ho SH, Lerner H, Thome JJC, Connors T, Reizis B, Farber DL. Dendritic Cells Display Subset and Tissue-Specific Maturation Dynamics over Human Life. Immunity. 2017;46(3):504—515. DOI: 10.1016/j.immuni.2017.02.019.

18. Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. Nat. *Immunol*. 2015;16:343—53. DOI: 10.1038/ni.3123.

19. Jongbloed SL, Lebre MC, Fraser AR, Gracie JA, Sturrock RD, Tak PP, McInnes IB. Enumeration and phenotypical analysis of distinct dendritic cell subsets in psoriatic arthritis and rheumatoid arthritis. *Arthritis Res Ther*. 2006;8(1): R15. DOI: 10.1186/ar1864.

20. Chrisikos TT, Zhou Y, Slone N, Babcock R, Watowich SS, Li HS. Molecular regulation of dendritic cell development and function in

homeostasis, inflammation, and cancer. *Mol Immunol*. 2019;110:24—39. DOI: 10.1016/j.molimm.2018.01.014

21. Ehrentraut S, Sauss K, Neumeister R, Luley L, Oettel A, Fettke F, Costa S-D, Langwisch S, Zenclussen AC and Schumacher A (2019) Human Miscarriage Is Associated With Dysregulations in Peripheral Blood-Derived Myeloid Dendritic Cell Subsets. *Front. Immunol*. 10:2440. DOI: 10.3389/fimmu.2019.02440

22. Sarkar S, Fox DA. Dendritic cells in rheumatoid arthritis. Front Biosci. 2005 Jan 1;10:656—65. doi: 10.2741/1560. PMID: 15569606

23. Falaleeva SA, Kurilin VV, Shkaruba NS, Chumasova OA, Sizikov AE, Sennikov SV. Subtype characterics of dendritic cells from peripheral blood of patients with rheumatoid arthritis. *Medical Immunology*. 2013;15(4):343—350.

24. Steinman RM. Decisions about dendritic cells: past, present, and future. Annu. Rev. *Immunol*. 2012;30:1—22.

25. Riol-Blanco L, Sánchez-Sánchez N, Torres A, Tejedor A, Narumiya S, Corbí AL, Sánchez-Mateos P, Rodríguez-Fernández JL. The chemokine receptor CCR7 activates in dendritic cells two signaling modules that independently regulate chemotaxis and migratory speed». *Journal of Immunology*. 2005;174(7):4070—80. DOI: 10.4049/jimmunol.174.7.4070

26. Ohl L, Mohaupt M, Czeloth N, Hintzen G, Kiafard Z, Zwirner J, et al. CCR7 governs skin dendritic cell migration under inflammatory and steady-state conditions. *Immunity*. 2004;21:279—88. DOI: 10.1016/j.immuni.2004.06.014

27. Kurobe H, Liu C, Ueno T, Saito F, Ohigashi I, Seach N, et al. CCR7-dependent cortex-to-medulla migration of positively selected thymocytes is essential for establishing central tolerance. *Immunity*. 2006;24:165—77. DOI: 10.1016/j.immuni.2005.12.011

28. Worbs T, Bode U, Yan S, Hoffmann MW, Hintzen G, Bernhardt G. Oral tolerance originates in the intestinal immune system and relies on antigen carriage by dendritic cells. *J Exp Med*. 2006;203:519—27. DOI: 10.1084/jem.20052016

29. Worbs T, Hammerschmidt SI, Förster R. Dendritic cell migration in health and disease. *Nat Rev Immunol*. 2017;17(1):30—48.

30. Ohta T, Sugiyama M, Hemmi H, Yamazaki C, Okura S, Sasaki I. Crucial roles of XCR1-expressing dendritic cells and the XCR1-XCL1 chemokine axis in intestinal immune homeostasis. *Sci Rep*. 2016;6:23505. DOI: 10.1038/srep23505

31. Kroczek RA, Henn V (2012). «The Role of XCR1 and its Ligand XCL1 in Antigen Cross-Presentation by Murine and Human Dendritic Cells». *Frontiers in Immunology*. 3: 14. doi:10.3389/fimmu.2012.00014

32. Alexandre YO, Ghilas S, Sanchez C, Le Bon A, Crozat K, Dalod M. XCR1+ dendritic cells promote memory CD8+ T cell recall upon secondary infections with Listeria monocytogenes or certain viruses. *J Exp Med*. 2016;213(1):75—92. DOI: 10.1084/jem.20142350

33. Lei Y, Ripen AM, Ishimaru N, Ohigashi I, Nagasawa T, Jeker LT, Bösl MR, Holländer GA, Hayashi Y, Malefyt Rde W, Nitta T, Takahama Y. Aire-dependent production of XCL1 mediates medullary accumulation of thymic dendritic cells and contributes to regulatory T cell development. *The Journal of Experimental Medicine*. 2011. 208(2):383—94. DOI:10.1084/jem.20102327

34. Denning TL, Norris BA, Medina-Contreras O, Manicassamy S, Geem D, Madan R, KarpC L, Pulendran B. Functional specializations of intestinal dendritic cell and macrophage subsets that control Th17 and regulatory T cell responses are dependent on the T cell/APC ratio, source of mouse strain, and regional localization. *J Immunol*. 2011;187(2):733—747. DOI:10.4049/jimmunol.1002701

35. Lehmann J, Huehn J, de la Rosa M, Maszyna F, Kretschmer U, Krenn V, Brunner M, Scheffold A, Hamann A. Expression of the integrin alpha Ebeta 7 identifies unique subsets of CD25+ as well as CD25- regulatory T cells. *Proc Natl Acad Sci USA*. 2002;99(20):13031—6. DOI:10.1073/pnas.192162899

36. Johansson-Lindbom B, Svensson M, Pabst O, Palmqvist C, Marquez G, Förster R, Agace WW. Functional specialization of gut CD103+ dendritic cells in the regulation of tissue-selective T cell homing. *J. Exp. Med*. 2005;202(8):1063—73. DOI: 10.1084/jem.20051100

37. Allakhverdi Z, Fitzpatrick D, Boisvert A, Baba N, Bouguermouh S, Sarfati M, Delespesse G. Expression of CD103 identifies human regulatory T-cell subsets. *J. Allergy Clin. Immunol*. 2006;118(6):1342—9. doi:10.1016/j.jaci.2006.07.034

38. del Rio ML, Bernhardt G, Rodriguez-Barbosa JI, Förster R. Development and functional specialization of CD103+ dendritic cells. *Immunol Rev*. 2010;234(1):268—81. DOI: 10.1111/j.0105-2896.2009.00874.x

39. Ho AW, Prabhu N, Betts RJ, Ge MQ, Dai X, Hutchinson PE, et al. Lung CD103+ dendritic cells efficiently transport influenza virus to the lymph node and load viral antigen onto MHC class I for presentation to CD8 T cells. *J Immunol*. 2011;187:6011—21. DOI: 10.4049/jimmunol.1100987

40. Helft J, Manicassamy B, Guermonprez P, Hashimoto D, Silvin A, Agudo J. Cross-presenting CD103+ dendritic cells are protected from influenza virus infection. J Clin Invest. 2012;122:4037—47. DOI: 10.1172/JCI60659

41. Xiao Y, Li H, Mao L, Yang QC, Fu LQ, Wu CC, Liu B, Sun ZJ. CD103+ T and Dendritic Cells Indicate a Favorable Prognosis in Oral Cancer. *Journal of Dental Research*. 2019:002203451988261. DOI: 10.1177/0022034519882618

42. Denning TL, Wang YC, Patel SR, Williams IR, Pulendran B. Lamina propria macrophages and dendritic cells differentially induce regulatory and interleukin 17-producing T cell responses. *Nat Immunol*. 2007;8:1086—1094.

43. Rescigno M, Urbano M, Valzasina B, Francolini M, Rotta G, Bonasio R, Granucci F, Kraehenbuhl JP, Ricciardi-Castagnoli P. Dendritic cells express tight junction proteins and penetrate gut epithelial monolayers to sample bacteria. *Nat Immunol*. 2001;2:361—367.

44. Meshcheryakova E, Guryanova S, Makarov E, Alekseeva L, Andronova T, Ivanov V. Prevention of experimental septic shock by pretreatment of mice with muramyl peptides. Int Immunopharmacol. 2001;1(9—10):1857—65. DOI: 10.1016/s1567-5769(01)00111-4.

45. Khaitov RM, Pinegin BV, Butakov AA. Immunotherapy of infectious postoperative complications using a new immunostimulant glycopin. *Immunology*. 1994;2:47—50.

46. Colbey, C., Cox, A.J., Pyne, D.B. et al. Upper Respiratory Symptoms, Gut Health and Mucosal Immunity in Athletes. *Sports Med*. 2018;48:65—77. https://doi.org/10.1007/s40279-017-0846-4

47. Engebretsen L, Soligard T, Steffen K. Sports injuries and illnesses during the London Summer Olympic Games 2012. Br *J Sports Med*. 2013;47:407—14.

48. Palmer-Green D, Elliott N. Sports injury and illness epidemiology: Great Britain Olympic Team (TeamGB) surveillance

during the Sochi 2014 Winter Olympic Games. *Br J Sports Med*. 2014;49:25—9.

49. Gleeson M, Pyne DB. Respiratory inflammation and infections in high-performance athletes. *Immunol Cell Biol*. 2016;94:124—31.

50. Smith AP. Effects of the common cold on mood, psychomotor performance, the encoding of new information, speed of working memory and semantic processing. *Brain Behav Immun*. 2012;26:1072—6.

51. Smith A. A review of the effects of colds and influenza on human performance. *J Soc Occup Med*. 1989;39:65—8.

52. Guryanova, S.V., Khaitov R.M. Glucosaminyl muramy ldipeptide in treatment and prevention of infectious diseases. *Infectious Diseases: News, Opinions, Training*. 2020;9(3):79—86. DOI: 10.33029/2305-3496-2020-9-3-79-86 (in Russian)

[*Гурьянова С.В., Хаитов Р.М.* Глюкозаминилмурамилдипептид в терапии и профилактике инфекционных заболеваний // Инфекционные болезни: новости, мнения, обучение. 2020. Т. 9. № 3. С. 79—86.]

Современные методы увеличения сопротивляемости острым респираторным инфекциям

С.В. Гурьянова[1, 2], Н.А. Кудряшова[3], А.А. Катаева[1], Б.Т. Орозбекова[4], Н.В. Колесникова[5], А.Г. Чучалин[6]

[1] Институт биоорганической химии им. академиков М.М. Шемякина и Ю.А. Овчинникова Российской академии наук, *г. Москва, Российская Федерация*

[2] Российский университет дружбы народов, *г. Москва, Российская Федерация*

[3] Институт Биохимической Физики им. Н.М. Эмануэля Российской академии наук, *г. Москва, Российская Федерация*

[4] Кыргызская государственная академия физической культуры и спорта, *г. Бишкек, Кыргызстан*

[5] Кубанский государственный медицинский университет, *г. Краснодар, Российская Федерация*

[6] Российский национальный исследовательский медицинский университет имени Н.И. Пирогова, *г. Москва, Российская Федерация*

✉ svgur@mail.ru

Аннотация. *Актуальность*. Респираторные инфекции являются наиболее распространенными в мире. В целях предотвращения эпидемий возникает необходимость в совершенствовании стратегий организации медицинской помощи и разработке новых подходов с целью повышения неспецифической резистентности организма, мобилизации врожденного иммунитета. *Целью* настоящего исследования явилось изучение влияния глюкозаминилмурамилдипептида (ГМДП) на уровень экспрессии маркеров дифференцировки и активации функционально значимых субпопуляций дендритных клеток в мононуклеарных клетках периферической крови здоровых доноров, а также оценка эффективности ГМДП при профилактике острых респираторных инфекций в не благоприятный эпидемиологический период. *Материалы и методы*. Открытое сравнительное исследование включало 309 условно здоровых участников, возраст 19—22 года. На первом этапе исследования 42 участника (22 девушки и 20 юношей) принимали в течение 10 дней препарат ликопид 1 мг согласно инструкции по 1 таблетке 3 раза в день с целью профилактики острых респираторных инфекций. Отбор периферической крови производили до приема препарата (день 0) и на следующий день после последнего приема препарата (день 12-й). Оценку экспрессии маркеров дифференцировки и активации субпопуляций дендритных клеток HLA-DR, CD11c, CD123, CD80, CD83, CCR7, CD3, CD14, CD20 оценивали методом проточной цитометрии. Параллельно выделяли мРНК из мононуклеарных клеток перриферической крови и после обратной транскрипции определяли уровень экспрессии генов методом RT PCR. На следующем этапе оценивалась эффективность профилактического применения препарата ликопид у 267 студентов Института физической культуры с целью предотвращения острых респираторных инфекций в не благоприятный эпидемиологический период, период наблюдения составил 12 месяцев. *Результаты и обсуждение*. Исследование относительного количественного состава ДК в периферической крови здоровых доноров

методом проточной цитометрии выявило возможность увеличения их общего количества, а также субпопуляций МДК и ПДК под действием ГМДП. Наблюдалось статистически значимое повышение рецепторов хемокина CCR7, ответственного за рекрутирование ДК во вторичные лимфоидные органы. Анализ уровней экспрессию генов XCR1, CD11b и CD103 показал статистически значимый эффект воздействия ГМДП на увеличение их экспрессии по сравнению с исходным уровнем (до приема ГМДП), причем среднее значение оказалось выше у участников эксперимента, испытывающих умеренные физические нагрузки. Обнаружено, что применение препарата ликопид 1мг с целью профилактики и снижения сезонной заболеваемости ОРЗ на этапе базовой подготовки спортсменов способствовало снижению заболеваемости ОРЗ в течение 12 месяцев наблюдения после приема препарата. Количество эпизодов ОРЗ в анамнезе уменьшилось в 3,7 раз, при этом полностью исчезла группа с 3 и более эпизодами ОРЗ в течение года, составлявшая 14.5 % спортсменов. Наибольшая эффективность ГМДП наблюдалась в группе легкой атлетики, в которой количество участников исследования, не имевших эпизодов ОРЗ в течение года, увеличилось в 7 раз. *Выводы*. Полученные данные дополняют современные представления молекулярного механизма действия ГМДП и обосновывают возможность его экспериментального и клинического применения для разработки новых стратегий организации медицинской помощи с целью повышения неспецифической резистентности организма.

Ключевые слова: врожденный иммунитет, глюкозаминилмурамилдипептид, ГМДП, мукозальный иммунитет, профилактика, острые респираторные инфекции, дендритные клетки, CD80, CD83, CCR7, CD103, XCR1, CD11b

Вклад авторов: С.В. Гурьянова и Н.В. Колесникова — разработка дизайна исследования; С.В. Гурьянова, Н.А. Кудряшова и А.А. Катаева — исследования методами проточной цитометрии и RT PCR; Б.Т. Орозбекова — клиническое наблюдение; С.В. Гурьянова, Н.В. Колесникова, Б.Т. Орозбекова — подготовка рукописи; А.Г. Чучалин — редактирование рукописи.

Информация о конфликте интересов. Авторы декларируют отсутствие конфликта интересов.

Поступила 09. 06. 2021. Принята 30. 07. 2021.

Для цитирования: *Guryanova S.V., Kudryashova N.A., A.A. Kataeva, Orozbekova B.T., Kolesnikova N.V., Chuchalin A.G.* Novel approaches to increase resistance to acute respiratory infections // Вестник Российского университета дружбы народов. Серия: Медицина. 2021. Т. 25. № 3. С. 181—195. doi: 10.22363/2313-0245-2021-25-3-181-195

Corresponding author: Svetlana V. Guryanova — PhD, Research Scientist, Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences, RUDN University, 177997, ul. Miklukho-Maklayay, 16/10, Moscow, Russian Federation. E-mail: svgur@mail.ru

Guryanova S.V. ORCID 0000-0001-6186-2462
Kolesnikova N.V. ORCID 0000-0002-9773-3408
Chuchalin A.G. ORCID 0000-0002-6808-5528

Ответственный за переписку: Гурьянова Светлана Владимировна — кандидат биологических наук, научный сотрудник ФГБУН «Институт биоорганической химии им. акад. М.М. Шемякина и Ю.А. Овчинникова» РАН, Российский университет дружбы народов, Российская Федерация, 117997, Москва, ул.Миклухо-Маклая 16/10. E-mail: svgur@mail.ru

Гурьянова С.В. SPINкод: 6722-8695; ORCID 0000-0001-6186-2462
Колесникова Н.В. ORCID 0000-0002-9773-3408
Чучалин А.Г. ORCID 0000-0002-6808-5528