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Expression of inflammation-related genes in mouse spleen under tuftsin analog Selank

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ABSTRACT

Previous studies have shown that synthetic tuftsin analogue Selank causes a transcriptomic response in the rat hippocampus and in spleen cells and may participate in the regulation of inflammatory processes in the body. In this work we studied the effect of Selank and two of its fragments on the expression of genes involved in processes of inflammation. We analyzed the expression of 84 genes involved in processes of inflammation (e.g., chemokines, cytokines, and its receptors) in mouse spleen 6 and 24 h after Selank single intraperitoneal injection (100 μg/kg) using real-time PCR method. We found significant changes in the expression of 34 genes involved in inflammation processes. The detailed analysis of quantitative data showed that the *Bcl6* gene, which plays a main role in the formation and development of the immune system, exhibited significant changes in its expression levels in response to injection of each of the peptides. Also, we observed expression changes for *Bcl6* target and corepressor genes under the influence of Selank and its fragments. Our results showed that Selank and its fragments caused a number of alterations in the expression of genes involved in inflammation. The data obtained confirmed the participation of Selank in the processes of regulation of inflammation in the body. The complex biological effect of Selank may be partially determined by the systematic effect of this peptide on genomic expression.

1. Introduction

The use of new drugs based on endogenous regulatory peptides is one of the main and the most perspective directions for therapy and prevention of various diseases, because of their natural origin, peptide regulators are believed to act directly with minimal side effects.

Physiologically active peptide compounds within the large family of the immunotropic peptide tuftsin (the first immune peptide with a distinct influence on the functions of the central nervous system) can be attributed to this class of drugs [1]. Tuftsin is a tetrapeptide (Thr-Lys-Pro-Arg) corresponding to the amino-acid sequence at position 289–292 of the CH2 domain of the Fc fragment of leucokinin isolated from the leucophilic fraction of IgG [2]. The principal biological activity of tuftsin consists of the activation of phagocytosis and cell migration. It improves communication between components of the immune system (macrophages, T cells, and antibody-producing B cells) and enhances the immune response against tumors [3,4].

Researchers from the Institute of Molecular Genetics of the Russian Academy of Sciences used the endogenous tuftsin molecule as the basis for the production of a new synthetic derivative – the neurotropic agent Selank. To improve its metabolic stability and its relatively long duration, the tuftsin peptide was elongated at the C terminus via the addition of three natural L-amino acids (Pro-Gly-Pro) [5–7]. In comparison with its precursor, Selank influences the immunological system more weakly but possesses a much stronger and longer central activity, which could be explained by its biochemical features [8]. Previous studies have shown that the peptide Selank has psychotropic functions that consist of a combination of anxiolytic and stimulatory actions, with no side effects [9–11].

Biochemical studies established that single doses of Selank produce significant changes in the levels of noradrenaline, dopamine,

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serotonin, and their metabolites in the brains of rats [12]. Furthermore, it was shown that Selank significantly inhibits enkephalin-degrading enzymes in human blood plasma [13,14]. Taking into account that the short half-life of blood enkephalins in patients with generalized anxiety disorders is determined by the relatively low concentration of endogenous enzyme inhibitors, this property of Selank probably underlies the mechanisms of its anxiolytic effect [10,15,16].

Experiments on rats have shown that Selank has significant positive effects on learning and memory processes. The results obtained in experiments performed on rats with normal and functionally decreased learning abilities using the active avoidance conditioned reflex method showed that the peptide compound Selank, administered at a dose of 300 μg/kg, improved learning parameters significantly in both groups of animals [17].

Furthermore, together with the properties described above, Selank influences the immune system. The antiviral activity of Selank against the influenza A virus (H_3N_2) was studied using *in vitro* and *in vivo* systems. Both systems revealed the presence of an antiviral effect for the drug. The introduction of Selank *in vivo* induces the expression of the *IFN-α* gene, without affecting the expression of the *IL-4*, *IL-10*, and *TNF-α* genes. The mechanism underlying the antiviral action of Selank is probably linked to its ability to modulate the balance of the Th1/Th2 cytokines [18].

Recent studies have shown that glyprolines have their specific physiological action. Thus supposes that the synthetic regulatory peptides, such as Semax and Selank have hybrid physiological properties, which that combine the properties of their structural components [5]. Study of antiviral properties of the structural fragments of the peptide Selank allowed selecting Gly-Pro as the minimum amino acid sequence (pharmacophore) has a pronounced antiviral effect. Also showed that among the studied fragments of Selank the highest antiviral activity against the human influenza A/Aichi 2/68 virus (H_3N_2), the human influenza B/Ohio 01/05 virus, the avian influenza virus (H_5N_1), the herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), the cytomegalovirus (CMV) and the murine encephalomyocarditis virus (EMCV) had tetrapeptide Arg-Pro-Gly-Pro [19].

In previous studies we analyzed the expression profiles of 12,000 genes in the rat hippocampus using microtemplates, performed a search for genes that exhibited differential expression under the action of Selank, and assessed the expression of selected genes in the rat spleen. We showed that Selank impacts the expression of the *Cx3cr1* gene encodes a specific receptor for the fraktalkin protein, which is involved in the maturation, transport, and recycling of leukocytes, as well as in the initiation of local inflammation. The expression of this gene was increased by 16 times in the spleen of rats 1 h after a single intranasal administration of Selank. These data indicate that Selank participates in the regulation of inflammatory processes in the body [20].

To obtain more detailed information on the impact of Selank on the body, here we aimed to study the influence of the Selank peptide and two of its fragments, Gly-Pro and Arg-Pro-Gly-Pro on the expression of genes involved in processes of inflammation.

We chose to study the mouse as the most suitable model for immunological studies, and the spleen because this tissue is a main immunity organ.

2. Materials and methods

2.1. Chemicals

Dry preparations of GP (Gly-Pro), RPGP (Arg-Pro-Gly-Pro), and Selank (Thr-Lys-Pro-Arg-Pro-Gly-Pro) were dissolved to a concentration of 20 μg/ml in saline solution.

2.2. Animal models

The males white mongrel mice (20 g) used in our experiments were kept under a 12 h light/dark cycle with free access to water and food. The animals were divided into 10 groups: five control ($n=10$ per group) and five experimental ($n=24$ per group) groups for each of the time points. Each experimental group was divided into three subgroups ($n=8$ per subgroup), according to the number of peptides administered. All groups were handled in the middle of the light phase of the diurnal cycle every day for 10 days. After this period of preparation, all control groups were treated with saline solution (single intraperitoneal injection) and the corresponding experimental groups were treated with a saline solution containing Selank or one of its two fragments (100 μg/kg, single intraperitoneal injection). The animals were decapitated 30 min, 90 min, 3 h, 6 h, and 24 h after the treatment (all animals of one control and one experimental group per time point).

The animal experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23), revised in 1996.

2.3. Sample preparation

Mouse spleens were removed immediately and tissue samples were immediately frozen and kept at −70 °C.

2.4. RNA isolation and reverse transcription

Total RNA was extracted from mouse spleen using the RNeasy® Mini Kit (Qiagen, Israel) and treated with RNase-free DNase I (Fermentas, Lithuania). Single-stranded cDNAs were synthesized using the RevertAid™ H Minus First-Strand cDNA Synthesis Kit (Fermentas, Lithuania). Individual cDNA samples were then combined into one sample for each group.

2.5. Real-time quantitative RT-PCR

The effect of Selank and some of its fragments on the expression of genes involved in processes of inflammation was studied using an RT^{2}Profile™ PCR Array Mouse Inflammatory Cytokines and Receptors panel (SABioscience, USA) containing 84 genes from different functional groups (e.g., chemokines, cytokines, and its receptors). The level of expression of certain genes was quantitated using real-time PCR in a StepOnePlus™ Real-Time qPCR System (ABI, USA) using the SYBR Green I dye (Syntol, Russia) and RT^2 qPCR Primer Assay SYBR® Green primers (SABioscience, USA). Thermal cycling was carried out as follows: (1) 95 °C for 600 s, followed by (2) 40 cycles of 15 s at 95 °C and 60 s at 60 °C.

All reactions were repeated three times for the cDNAs in each experimental and control groups for each time point using specific gene primers.

2.6. Statistical analyses

Statistical data analysis was performed using the Relative Expression Software Tool-384 version 2 (REST-384) [21–23]. The threshold reaction cycle (*Ct*) values for certain genes were normalized to the *Ct* values of the four reference housekeeping genes: *Actb*, *Gapdh*, *Hprt1*, and *Hsp90ab1*.

3. Results

3.1. Action of Selank and its fragments on the expression of genes involved in processes of inflammation

In the first stage, we analyzed the expression of 84 genes involved in inflammation processes. Alterations in gene expression were analyzed in the mouse spleen 6 and 24 h after a single intraperitoneal injection of peptides (100 μg/kg).

We found significant changes ($p \leq 0.05$) in the expression of 34 genes from different functional groups: chemokines, chemokine receptors, cytokines, cytokine receptors, and other genes involved in inflammation processes (Table 1). We showed that a single intraperitoneal injection of Selank led to a change in the mRNA levels of 16 genes. A change in the expression of most of the genes under study was observed after a single injection of Gly-Pro, which led to an alteration in the mRNA level of 22 genes. It should be noted that Gly-Pro led to a response in the greatest number of genes under study 6 h after injection. In contrast, a change in the expression of many genes was observed 24 h after injection of Selank.

Table 1 shows that some of the genes analyzed exhibited significant changes ($p \leq 0.05$) in its mRNA level in response to the injection of each of the peptides. For example, alterations in the mRNA level of the *Il2rg* gene, which belongs to the family of cytokine receptors, were noted as early as 6 h after a single injection of Selank or of its two fragments. In contrast, changes in the mRNA level of the *Xcr1* gene, which belongs to the family of chemokine receptors, were observed only 24 h after injection of the peptides. Among other genes involved in inflammation, the *C3*, *Casp1*, and *Bcl6* genes also exhibited significant alterations in expression level in response to the injection of each of the studied peptides. Injection of Gly-Pro and Arg-Pro-Gly-Pro led to a change in the mRNA levels of the *C3* and *Casp1* genes 6 h after injection, whereas the mRNA level of the *Bcl6* gene changed 24 h after injection of the peptides. It should be noted that the injection of Selank caused a change in the mRNA levels of the *Bcl6* and *Casp1* genes both 6 h and 24 h after injection.

3.2. The temporal dynamics of Bcl6 gene expression under the action of Selank and its fragments

The detailed analysis of quantitative data showed that the *Bcl6* gene, which plays a main role in the formation and development of the immune system, exhibited significant changes in its expression levels in response to injection of each of the peptides. It should be noted that after the Selank administration changes in the mRNA level of this gene is observed both at 6 and 24 h after a single injection of peptide. *Bcl6* encodes a nuclear transcriptional repressor that is involved in the development of the germinal center and participates in the regulation of the development, differentiation, and survival of lymphocytes and in the differentiation and activation of B and T cells and macrophages [24].

Based on this, this gene was selected for additional and more detailed analysis. To do this, we engaged in the second stage of our study. We analyzed the temporal dynamics of the expression of the *Bcl6* gene under the action of Selank or its fragments. For this analysis, we selected five time points: 30 min, 90 min, 3 h, 6 h, and 24 h.

We established that, in general, the injection of Selank or its fragments yielded a similar pattern of changes in the levels of expression of the *Bcl6* mRNA (Fig. 1). At an early stage (<3 h after the injection of the peptides), we observed a significant increase in the expression of the *Bcl6* transcript 90 min after Selank injection and a decrease in the expression of the *Bcl6* mRNA after injection of Gly-Pro and Arg-Pro-Gly-Pro. In contrast, an overall decrease in the level of the *Bcl6* mRNA was observed 3 h after injection of each of the peptides. After 6 h, we found a significant increase in the level of the *Bcl6* transcript, which was strongest after the injection of Gly-Pro and Arg-Pro-Gly-Pro (4.9 and 4.4 times, respectively).

Table 1
Genes significantly altered the expression under the action of Selank and its fragments.[a]

Peptides						
Gene groups	Selank		Gly-Pro		Arg-Pro-Gly-Pro	
	6 h	24 h	6 h	24 h	6 h	24 h
Chemokine	*Ccl17*	*Ccl7* *Ccl19* *Cxcl15*	*Ccl3* *Ccl17* *Ccl20* *Cxcl10* *Cxcl12*	*Ccl11*	*Cxcl10* *Cxcl12*	*Ccl5* *Ccl20*
Chemokine receptors	–	**Xcr1**	*Ccr2* *Ccr4*	**Xcr1**	–	**Xcr1**
Cytokine	*Ifng*	*Il1f8* *Il20*	*Il10* *Itgam* *Scye1*	*Il20* *Itgam* *Itgb2*	*Il16* *Itgam*	*Itgb2*
Cytokine receptors	*Il1r2* **Il2rg**	*Il1r2* *Il5ra* *Il13ra1*	*Il1r2* **Il2rg**	–	**Il2rg**	–
Other genes	**Bcl6** *Blr1* **C3** **Casp1**	**Bcl6** **Casp1**	**C3** **Casp1** *Cpr*	*Abcf1* **Bcl6** *Tollip*	*Blr1* **C3** **Casp1**	**Bcl6** *Mif* *Tgfb1*

The genes with changed mRNA level after the injection of each of the peptides marked in bold.
[a] $p \leq 0.05$.

3.3. The temporal dynamics of Bcl6 target genes expression under the action of Selank and its fragments

To perform a more detailed assessment of the dynamics of the expression of the *Bcl6* gene, we analyzed the changes in the expression of its target genes under the influence of Selank or its fragments. We selected five genes from three of the functional groups: genes involved in cell-cycle control and apoptosis (*Ccnd1* and *Ccnd2*); genes involved in the processes of differentiation and activation of B cells (*Cd44* and *Cd69*); and one gene involved in the processes of differentiation and activation of T cells and macrophages (*Stat1*).

Table 2 depicts the multidirectional activation of the expression of the genes under investigation over different intervals after injection of Selank or its fragments.

We established that Selank injection caused a rapid response of the genes under study (<3 h after the injection of peptides) and had virtually no influence on the levels of gene expression at later time points. The *Stat1* gene exhibited the most active response to Selank injection. At first, we observed an increase in the level of the *Stat1* mRNA 30 and 90 min after injection (1.3 and 1.7 times, respectively). Subsequently, its expression was decreased by 1.2-fold 3 h after the injection. It should be noted that the pattern of changes in the level of the *Stat1* mRNA was very similar to the pattern of changes observed for the *Bcl6* mRNA at the time points selected after injection of Selank (Fig. 1).

We also established that injection of Gly-Pro exerted the most active effect on the expression of *Bcl6* target genes, as it caused an early response for all *Bcl6* target genes under study. At a late stage (>3 h after Selank injection), we observed the activation of only one gene (*Cd69*; its mRNA level was decreased by 2.3 times).

Injection of Arg-Pro-Gly-Pro had the strongest effect on the level of mRNA of genes involved in cell-cycle control and apoptosis (*Ccnd1* and *Ccnd2*). It should be noted that these changes were observed at early time points, whereas an expression peak was observed for *Ccnd2* 6 h after peptide injection (5-fold increase in expression compared with the control).

3.4. The temporal dynamics of expression of gene-corepressors BCL6 protein under the action of Selank and its fragments

Together with *Bcl6* target genes, we evaluated the corepressors *Bcor*, *Ncor1*, and *Ncor2*, which are necessary to ensure the

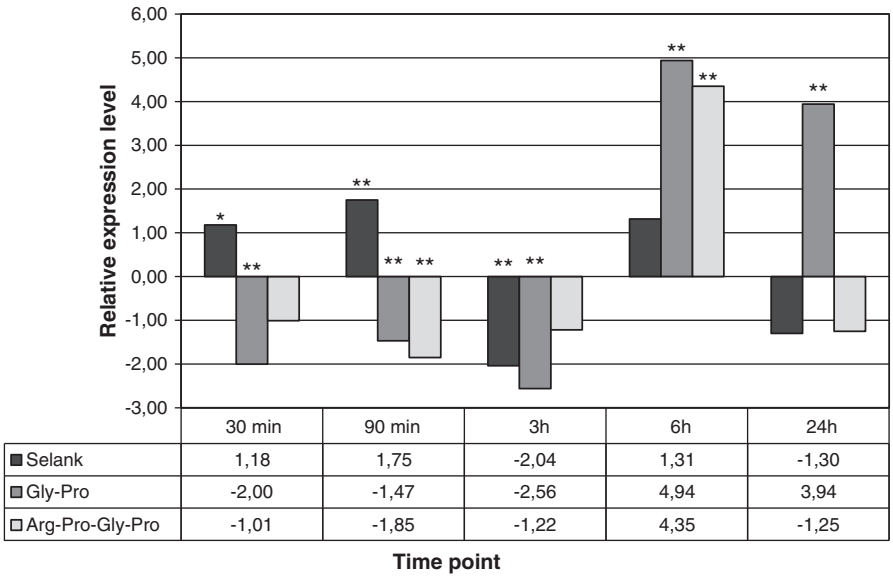

Fig. 1. The temporal dynamics of *Bcl6* gene expression under the action of Selank and its fragments (* $p \leq 0.05$; ** $p \leq 0.01$).

communication of the transcriptional repressor BCL6 with its targets (Table 3).

We observed a similar pattern of changes in expression levels of the *Bcor* and *Ncor1* genes 30 min, 90 min, and 3 h after the injection of Selank and Gly-Pro. In addition, the level of expression of these transcripts decreased 30 min and 3 h after the injection of peptides and increased 90 min after injection. The greatest increase in the expression of the *Ncor2* mRNA was observed 30 min after Selank injection (7.2 times) and 24 h after injection of Gly-Pro (4.1 times). Injection of Arg-Pro-Gly-Pro caused a significant decrease in the expression of the *Ncor2* gene exclusively, at early time points.

4. Discussion

Selank is a synthetic peptide that is an analogue of tuftsin (the short Thr-Lys-Pro-Arg fragment of the human IgG heavy chain). Selank is elongated at the C terminus with the tripeptide Pro-Gly-Pro and exhibits a dual effect on organisms: it has nootropic and anxiolytic characteristics and exhibits an antiviral action. However, the mechanisms of action of this peptide remain unclear.

In this study, we evaluated the impact of Selank and its fragments on the expression of genes involved in inflammation processes. We found that the significant changes ($p \leq 0.05$) in mRNA expression levels after injection of each of the peptides were observed for the *Xcr1* gene, which encodes a receptor for the XCL1 chemokine (activator of the chemotactic activity of lymphocytes) [25], and for the *Il2rg* gene, which encodes a common subunit of the receptors for a variety of interleukins (responsible for interleukin stimulation) [26].

Also the significant response to the injection of each of the peptides was observed for the *Bcl6*, *C3*, and *Casp1* genes. *Bcl6* exhibited the significant changes in its expression in response to the introduction of each of the peptides. Moreover, in response to the introduction of Selank the expression of this gene is observed both 6 h and a day after a single injection. The *Bcl6* gene encodes a nuclear sequence-specific transcriptional repressor composed of an N-terminal BTB domain and six zinc finger domains located at the C terminus [27]. These domains regulate the transcription of target genes via distinct interactions. Normally, the BCL6 protein serves as an important transcriptional regulator of the immune system. It is specifically required for the formation of the germinal center (GC) and is a critical negative regulator of Th2 responses. Increasing evidence

Table 2
The temporal dynamics of *Bcl6* target genes expression under the action of Selank and its fragments.[a]

Peptide	Time point	Genes				
		Ccnd1	Ccnd2	Cd44	Cd69	Stat1
Selank	30 min	1.25	1.13	−1.08	**1.47****	**1.37****
	90 min	1.23	**1.60****	**1.33****	−1.06	**1.77****
	3 h	1.07	2.16	−1.30	1.00	**−1.16****
	6 h	1.14	1.22	1.11	−1.14	1.16
	24 h	1.03	−1.06	**−1.59****	−1.18	−1.03
Gly-Pro	30 min	−1.23	−1.12	**−1.35****	−1.18	**−1.35****
	90 min	**1.82****	**1.40****	**1.95****	1.19	1.51
	3 h	**−1.45****	**1.62***	−1.14	**−1.47****	**−1.47****
	6 h	−1.61	−1.19	−1.14	−1.33	−1.28
	24 h	−1.67	−2.70	**−2.38****	−1.39	−1.35
Arg-Pro-Gly-Pro	30 min	**−1.85****	**−1.56****	−1.30	**−1.72****	−1.41
	90 min	1.27	1.33	1.22	−1.30	1.22
	3 h	**−1.28***	**2.13****	1.22	1.19	1.04
	6 h	1.84	**5.33****	1.74	−2.13	1.45
	24 h	1.29	1.52	1.46	1.23	−1.25

The genes with significant changes in mRNA level marked in bold.
[a] * $p \leq 0.05$; ** $p \leq 0.01$.

Table 3
The temporal dynamics of expression of gene-corepressors BCL6 protein under the action of Selank and its fragments.[a]

Peptide	Time point	Genes		
		Bcor	Ncor1	Ncor2
Selank	30 min	**−11.11****	**−1.14***	**7.20****
	90 min	**1.42****	**2.25****	−1.06
	3 h	**−2.08****	**−2.04****	**−6.25****
	6 h	−10.00	1.20	1.36
	24 h	−1.22	1.13	−1.20
Gly-Pro	30 min	**−1.33***	**−1.41****	**−2.86****
	90 min	**1.15***	**1.35****	**−3.33****
	3 h	**−1.64****	**−2.33****	**−4.00****
	6 h	−1.54	1.05	2.45
	24 h	−2.17	1.70	**4.09****
Arg-Pro-Gly-Pro	30 min	−1.18	1.04	**−1.45***
	90 min	−1.01	−1.10	**−11.11****
	3 h	−1.09	−1.08	**−1.51****
	6 h	−1.30	−1.15	1.34
	24 h	3.32	−1.15	−2.00

The genes with significant changes in mRNA level marked in bold.
[a] * $p \leq 0.05$; ** $p \leq 0.01$.

suggests that BCL6 plays a pivotal role in the regulation of B- and T-cell development by functioning as a potent transcriptional silencer of various developmental signals [28–30].

Studies show that murine *Bcl6* is expressed in lymphatic tissues, i.e., the thymus and spleen. The processes leading to differentiation of T and B lymphocytes are not known in detail. However, it is interesting to note that a high *Bcl6* signal was present in the cortex of the thymus, where T-cell proliferation takes place. A high *Bcl6* signal was also recorded over GC in the spleen, where B-cell proliferation occurs. Thus, it may be speculated that *Bcl6* has a function as a regulator of transcriptional activity during the differentiation process of cells of both T- and B-cell lineages. Results also show that *Bcl6* is expressed in several other types of tissues [31].

Our data show that the injection of GP led to the activation of the expression of this gene at 30 min, 90 min, 3 h, 6 h, and 24 h after injection. In addition, there was a marked drop in expression in the period up to 3 h after injection, which was replaced by an increase in expression 6 h after injection. In contrast to what was observed for GP, Selank activated the early-response gene *Bcl6* by increasing its level of expression in the first 30 and 90 min after injection. The greatest increase in expression was observed after the introduction RPGP (4.4 times). The most pronounced effect on the expression of *Bcl6* was exerted by GP.

BCL6 is implicated in antiapoptotic activity, by repressing the human programmed cell death-2 pathway [32], and in cell-cycle control, by repressing genes such *p27kip1*, *Ccnd1*, and *Ccnd2* [33]. BCL6 interacts with the transcription factor MIZ-1 to suppress *p21cdk1* and cell-cycle arrest in GC B cells [34].

The precise molecular mechanism by which BCL6 represses the transcription of these target genes remains unclear. A cis-acting element (a similar BCL6 consensus site) was found in the regulatory regions of several target genes (*Cd69*, *Cd44*, *Ccnd2*, and *Mip-1a*), which are all induced during the activation of mature B cells by BCR or mitogen [33].

The assessment of the impact of Selank and its fragments on the target genes of *Bcl6* showed that a change in the expression of the latter did not always correspond to a change in the expression of *Bcl6*. Thus, the expression levels of *Ccnd1* and *Ccnd2*, which participate in the processes of cell-cycle regulation, increased 90 min after the introduction of GP, whereas the level of expression of *Bcl6* was decreased. A similar result was obtained for *Ccnd2* 3 h after administration of GP. The expression of *Ccnd2* was increased 90 min after the injection of Selank, as was the expression of *Bcl6*. Injection of RPGP modified the expression of *Ccnd1* and *Ccnd2* significantly, whereas no significant changes were identified regarding the expression of *Bcl6*.

Similar changes were observed for the expression of *Cd44* and *Cd69*, which are involved in the maturation and differentiation of B cells. Published data show that increased levels of *Bcl6* lead to the inhibition of the expression of these genes [30]. This relationship was observed 90 min after the administration of GP; *Bcl6* expression was decreased by 1.5 times and the level of expression of *Cd44* was doubled increased by 2 times. In the other cases mentioned, there was a unidirectional change in the expression of both genes.

The *Stat1* gene is responsible for the activation of T cells and macrophages. Its expression levels change depending on changes in the expression of *Bcl6*.

Data obtained in this study suggest that the change in the expression of *Bcl6* target genes did not always correspond to changes in the expression of the *Bcl6* gene. Thus, we can assume that the activation of these genes may be associated not only with BCL6-linked paths, but also with an independent mechanism, the activation of which may be an indirect effect of Selank and its fragments.

BCL6 represses its target genes by recruiting corepressor proteins via its three different protein domains. The interactions between the BCL6 BTB domain, via its lateral groove, and a silencing mediator for retinoid and thyroid hormone receptors (SMRT), nuclear hormone receptor corepressor (NCoR), and additional corepressors, such as the BCL6-interacting corepressor (BCoR), are mutually exclusive and most likely compete for binding at this site [35]. Changes in the level of expression of genes encoding proteins that are members of this complex may affect the repression ability of *Bcl6*.

We analyzed the temporal dynamics of three genes that encode protein corepressors BCL6: *Ncor1*, *Ncor2*, and *Bcor*. The most active response of the selected genes was observed after the introduction of GP and Selank. The introduction of RPGP led to changes in the expression levels of the *Ncor2* gene exclusively. We noted that changes in mRNA levels corresponded to a change in the mRNA level of the corepressors of *Bcl6*.

Our results showed that Selank and its fragments caused a number of alterations in the expression of genes involved in inflammation. Furthermore, in some cases, significant activation of expression was observed even after 24 h after the injection of single peptides. The data obtained confirmed the participation of Selank in the processes of regulation of inflammation in the body.

GP was the most active among the peptides studied. Its introduction led to a quick response (from 30 min to 3 h) of the genes under study. We also observed the activation of some of these genes after 6 and 24 h. Thus, the dipeptide Gly-Pro can be assumed to be a minimum Selank fragment with a pronounced antiviral effect.

The complex biological effect of Selank may be partially determined by the systematic effect of this peptide on genomic expression. The mechanism described for the action of peptides provides new opportunities for directional changes of transcriptional profiles under the influence of oligopeptides that are homologues of natural, biologically active peptides. However, additional studies of the mechanisms of action of peptides, including Selank, in various body systems and processes are required.

Declaration of interest

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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