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ORIGINAL ARTICLE

INFLUENCE OF ONCOLYTIC STRAINS OF A NEW UNCLASSIFIED GROUP OF HUMAN ROTAVIRUSES ON PERIPHERAL BLOOD LYMPHOCYTES

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ABSTRACT

Purpose of the study. Evaluation of the cytotoxic effect of strains RVK100 and RVK228 of a new unclassified group of human rotaviruses on human peripheral blood mononuclear cells *in vitro*.
Materials and methods. As a material for the study, we used peripheral blood mononuclear cells of a healthy donor. The cells were exposed to two strains of rotaviruses RVK100 and RVK228 for 24 and 48 hours. The cytotoxicity of the tested viruses was assessed using the Colorimetric Cell Viability Kit I (WST-8) (PromoCell, Germany). Analysis of lymphocytes subpopulation composition was assessed on a FACSCantoII flow cytometer (BD, USA) using monoclonal antibodies to human antigens: CD3, CD4, CD8, CD16/56, CD19, CD45, CD38, HLA-DR.
Results. According to the cell viability test, there was no significant decrease in the number of living cells in the samples with the addition of viruses in comparison with the control. On the contrary, after 48 hours of cultivation in the samples with the addition of RVK228, the number of living cells was significantly higher than in the control. The study of lymphocytes subpopulation composition showed a relative increase in the number of early activation markers on T cells in samples with viruses, which was also more pronounced in samples with the addition of RVK228.
Conclusion. The investigated strains of rotaviruses have no cytotoxic effect on human peripheral blood mononuclear cells. Moreover, the RVK228 strain is likely to have the ability to activate lymphocytes.

Keywords:
oncolytic viruses, rotaviruses, peripheral blood mononuclear cells, cytotoxicity assay, flow cytometry.

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ВЛИЯНИЕ ОНКОЛИТИЧЕСКИХ ШТАММОВ НОВОЙ НЕКЛАССИФИЦИРОВАННОЙ ГРУППЫ РОТАВИРУСОВ ЧЕЛОВЕКА НА ЛИМФОЦИТЫ ПЕРИФЕРИЧЕСКОЙ КРОВИ

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РЕЗЮМЕ

Цель исследования. Оценка цитотоксического действия штаммов RVK100 и RVK228 новой неклассифицированной группы ротавирусов человека на мононуклеарные клетки периферической крови человека *in vitro*.
Материалы и методы. В качестве материала для исследования использовали мононуклеарные клетки периферической крови здорового донора. На клетки воздействовали двумя штаммами RVK100 и RVK228 в течение 24 и 48 часов. Цитотоксичность тестируемых вирусов оценивали с помощью теста Colorimetric Cell Viability Kit I (WST-8) (PromoCell, Германия). Анализ субпопуляционного состава лимфоцитов оценивали на проточном цитофлуориметре FACSCantoII (BD, США) с использованием панели моноклональных антител к человеческим антигенам: CD3, CD4, CD8, CD16/56, CD19, CD45, CD38, HLA-DR.
Результаты. По данным теста на жизнеспособность не было обнаружено достоверно значимого снижения количества живых клеток в образцах с добавлением вирусов по сравнению с контролем. Напротив, после 48 часов культивирования в образцах с добавлением RVK228 количества живых клеток было достоверно больше, чем в контроле. Исследование субпопуляционного состава лимфоцитов показало относительное увеличение количества маркеров ранней активации на Т-клетках в образцах с вирусами, которое также было более выражено в образцах с добавлением RVK228.
Заключение. Исследуемые штаммы ротавирусов не оказывают цитотоксического действия на мононуклеарные клетки периферической крови человека. При этом штамм RVK228, вероятно, обладает способностью к активации лимфоцитов.

Ключевые слова:
онколитические вирусы, ротавирусы, мононуклеарные клетки периферической крови, цитотоксический тест, проточная цитофлуориметрия.

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INTRODUCTION

Despite the success of modern oncology, malignant tumors are the second most common cause of death worldwide [1]. Oncolytic virotherapy is one of the antitumor strategies, the development of which remains relevant for a number of decades. The potential of oncolytic viruses (OV) was finally realized when the first drug for therapy based on OV – Oncorin (H101) – was approved by the State Food and Drug Administration of China (SFDA) for clinical use in the treatment of nasopharyngeal carcinoma in 2005 [2]. Later, in 2015, the US Food and Drug Administration (FDA) approved the drug T-Vec based on a modified herpes simplex virus (HSV) for the treatment of metastatic melanoma [3]. Both natural attenuated and engineered viruses that are nonpathogenic to humans are being studied all over the world. Identifying the most active and safe of them would allow us to offer new methods of treating malignant tumors.

The safety of the use of OV depends on their ability to infect and replicate only in tumor cells. It is known, in particular, that the selective replication of viruses in cancer cells is mainly due to impaired mechanisms of the antiviral response in transformed cells (for example, the type I interferon signaling pathway) [4]. Disorders of cellular metabolism [5] and signaling pathways regulating cell division [6] are also considered as possible reasons for the OV tropism to tumor cells. Since it is impossible to draw a conclusion about its safety only on the basis of data on the interaction of OV with tumor cells, a necessary stage in research to find new OV is testing their cytotoxic activity in relation to normal cells of the body.

In the Rostov Institute of Microbiology and Parasitology (the Rostov Research Institute of Microbiology and Parasitology of Rospotrebnadzor), during the work on the adaptation of group A human rotaviruses to growth on transplanted cell cultures for their use as a vaccine for children, strains that did not belong to any of the known groups of human rotaviruses were detected and isolated [7]. The new group is called group K rotaviruses (RVK), its representatives have common features both with group A rotaviruses, which are the most common pathogens of gastroenteritis in children, and with reoviruses. Further joint studies of the National Medical Research Centre for Oncology of the Ministry of Health of Russia and the Rostov Research Institute of Microbiology and Parasitology showed the oncolytic activity and immunomodulatory properties of this group of viruses in vivo and *in vitro* [8-10]. The future prospects of using new rotavirus strains in oncolytic virotherapy will be determined by their safety in relation to normal human cells.

The purpose of the study was to evaluate the cytotoxic effect of RVK100 and RVK228 viruses of a new unclassified group of human rotaviruses of the family Reoviridae on peripheral blood mononuclear cells of healthy donors.

MATERIALS AND METHODS

Oncolytic strains of rotaviruses

The study used two live attenuated, nonpathogenic rotavirus strains previously isolated at the Rostov Institute of Microbiology and Parasitology, with the working name rotaviruses of group K – RVK100 and RVK228 [7].

Cultivation of peripheral blood mononuclear cells

Peripheral blood mononuclear cells (MNCs) were obtained from a healthy male donor of 25 years. The donor signed an informed consent to participate in the study. Mononuclear cells were isolated by centrifugation using Vacutainer® CPT ™ tubes (BD, USA) according to the manufacturer's instructions. The resulting cells were counted with the addition of 0.4 % trypan blue on an automatic Eve counter (NanoEnTek Inc, Korea).

Determination of the cytotoxic activity of viruses

MNCs were introduced into a 96-well tablet (Eppendorf, Germany) in an equal seeding dose of 10^4 cells per well in 100 ml of RPMI 1640 nutrient medium (Gibco, USA) without the addition of serum and antibiotics. Then the cells were cultured for 24 hours at 37 °C in a humid atmosphere containing 5 % CO_2. After 24 hours, viruses were introduced into the wells with MNCs to a final concentration of 10^7 particles/ml, for which 1 ml of a suspension of viruses with a concentration of 10^9 particles/ml in the RPMI 1640 nutrient medium without serum was added to each well of the 96-well tablet. An equal amount of virus-free medium was introduced into

the control wells. Next, the MNCs were cultured for 24 or 48 hours at 37 °C in an atmosphere of 5 % CO_2. WST-8-the test used to determine cytotoxicity is an analog of the popular MTT test. The number of living cells was evaluated by colorimetric measurement of the concentration of formazan obtained during the reduction of WST-8 by cellular reductases. The study used the Colorimetric Cell Viability Kit I (WST-8) (PromoCell, Germany) according to the manufacturer's instructions. The optical density (OD) was measured using an ELISA reader Stat Fax2100 (Awareness Technology, USA) at a wavelength of 492 nm. Each variant of the experiment was put in 16 repeats, including 2 incubations and 2 strains.

Determination of the population composition of lymphocytes

For cytofluorimetric analysis, cells were introduced 5×10^5 cells per well of a 6-well tablet (Eppendorf, Germany) in 1.5 ml of RPMI 1640 nutrient medium without the addition of serum and antibiotics. The cultivation of cells with viruses was carried out as described above. The study of the population and subpopulation composition of lymphocytes was carried out on a 6-color flow cytometer BD FACSCanto II (Becton Dickinson, USA) using a panel of monoclonal antibodies to human antigens: CD3, CD4, CD8, CD16/56, CD19, CD45, CD38, HLA-DR (Becton Dickinson, USA).

Statistical analysis

The colorimetric test data is presented as an average value of ± 95 % confidence interval. The reliability of the difference between the average values was determined using the Student's t-test. The significance level adopted in the study, taking into account the Bonferroni correction for multiple comparison, was $\alpha' = \alpha/6 = 0.005/6 = 0.008$. The critical value of the Student's t-test for the adjusted $\alpha' = 0.008$ and $df = 2n-2 = 30$ was $t_{crit} = 2.84$.

RESEARCH RESULTS AND DISCUSSION

The addition of viruses to the culture medium did not have a cytotoxic effect on the MNC. According to the results of the colorimetric test, the level of living cells in both samples with the addition of viruses and in control samples did not differ significantly after 24 hours of cultivation (OD_{contr}=0.21±0.007, OD_{RVK100}=0.22±0.007, OD_{RVK228}=0.21±0.01). After 48 hours of cultivation, there was a significant decrease in the proportion of living cells in all samples, but in the sample with the addition of the RVK228 strain, the decrease was less pronounced (OD_{contr}=0.14±0.003, OD_{RVK100}=0.14±0.01, OD_{RVK228}=0.15±0.005) (Fig. 1). Testing the hypothesis of equality of mean values using the Student's t-test showed that the difference in the proportion of living cells between the control and

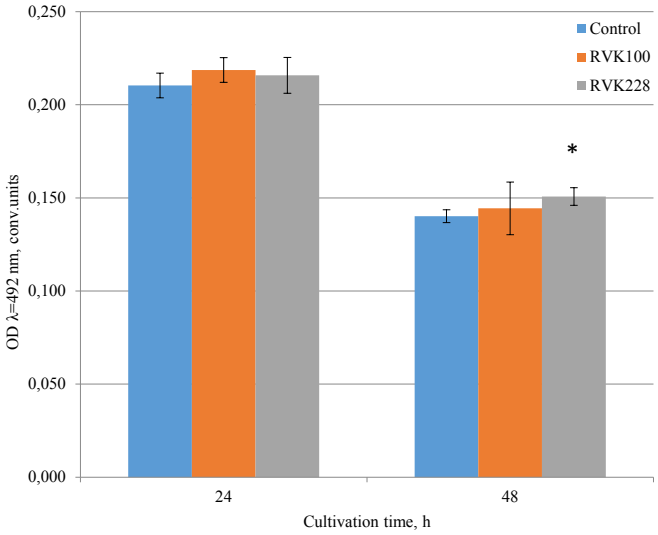

Fig. 1. The results of the WST-8 test under the action of oncolytic rotavirus strains RVK100 and RVK228 on MNCs under in vitro conditions (mean value ± 95% confidence interval). * – the difference in the average values compared to the control is statistically significant at the significance level α'≤0.008.

the variant with the addition of RVK228 is significant at the significance level α'≤0.008 (t_{exp}=3.53, df=30), while the differences between the other variants did not reach the accepted significance level.

A decrease in the proportion of living MNCs after a short period of time after passage indicates the death of some cells, probably caused by the absence of specific signals in the serum-free environment that support the activation and proliferation of lymphocytes [11]. The fact that the decrease in the level of living cells after 48 hours of cultivation in the sample with RVK228 was not as pronounced as in the control sample and in the sample with RVK100, may be due to the fact that this strain has a greater ability to activate cells of the immune system compared to RVK100. This assumption is supported by the results cytofluorimetric studies are shown in tables 1, 2.

It should be noted that incubation of donor samples MNC for 24 hours under these conditions without viruses has led to significant changes in their

Table 1. Effect of RVK100 and RVK228 strains on the population composition of lymphocytes under *in vitro* conditions

Samples	Lymphocyte populations, % of CD45+ (mean value ± standard deviation)			
	$CD3^+$	$CD19^+$	$CD16/56^+$	$CD3/16/56^+$
Before incubation	80.4±7.4	1.7±0.2	14.3±2.1	2.6±0.9
		24 hours		
Control	67.4±6.2	0.7±0.05	25.6±3.0	5.3±1.1
RVK100	72.1±8.0	0.9±0.1	24.4±2.8	4.1±1.0
RVK228	67.2±7.8	0.7±0.08	27.3±3.1	4.1±0.7
		48 hours		
Control	68.8±5.8	0.9±0.15	23.9±2.3	3.6±0.5
RVK100	68.3±7.1	0.4±0.03	25.6±3.05	2.5±0.5
RVK228	69.1±6.5	0.5±0.03	25.6±2.8	3.1±0.8

Table 2. Effect of RVK100 and RVK228 strains on the subpopulation composition of T-lymphocytes under *in vitro* conditions

Samples	T-lymphocyte subpopulations (mean value ± standard deviation)					
	$CD4^+$, % of $CD3^+$	$CD8^+$, % of $CD3^+$	$CD4^+HLA\text{-}DR^+$, % of $CD4^+$	$CD4^+CD38^+$, % of $CD4^+$	$CD8^+HLA\text{-}DR^+$, % of $CD8^+$	$CD8^+CD38^+$, % of $CD8^+$
Before incubation	38.1±4.8	38.0±5.1	6.4±0.9	33.8±3.8	10.4±1.8	10.7±2.1
			24 hours			
Control	15.8±2.1	39.6±3.5	17.0±1.3	12.8±1.7	4.3±3.1	3.8±0.45
RVK100	13.8±1.05	48.0±5.6	23.5±1.9	7.8±0.9	2.7±1.9	6.0±0.8
RVK228	13.2±1.4	39.5±4.2	19.6±2.1	13.7±1.2	6.0±0.7	8.8±0.74
			48 hours			
Control	14.0±1.7	40.8±4.02	20.5±2.5	9.5±1.05	2.3±0.4	4.5±0.6
RVK100	12.9±1.07	39.0±4.5	18.9±2.1	8.7±0.9	2.7±0.3	4.6±0.8
RVK228	11.2±1.5	39.9±3.8	21.3±2.8	14.7±1.9	3.5±0.7	3.5±0.4

composition: there was a decrease in the percentage of cells expressing $CD3^+$ and $CD4^+$, with preservation of the percentage of $CD8^+$, the marked increase in the percentage of NK-cells, which, apparently, was more resistant to such cultivation; the changes were made in subpopulations of activated T-cells.

After 24 hours, in both samples with the addition of viruses, compared with the cultivation control, there was a relative increase in the proportion of T-killers expressing an early activation marker ($CD8^+CD38^+$), while the reaction to RVK228 was more pronounced (RVK228 – 8.8 % ± 0.74 %, RVK100 – 6.0 % ± 0.8 %, control – 3.8 %±0.45 %). The 24-hour incubation of MNCs with RVK was also accompanied by an increase in the percentage of $CD4^+$ cells and a decrease in $CD8^+$ cells expressing $HLA\text{-}DR^+$ under the action of RVK100. After 48 hours of cultivation, the expression of the early activation marker on T-helpers ($CD4^+CD38^+$) exceeded the control values only in samples with the addition of RVK228 (RVK228 – 14.7 ± 1.9 %, RVK100 – 8.7 ± 0.9 %, control – 9.5 %±1.05 %).

There were no significant changes in the relative number of T-lymphocytes ($CD3^+$), T-killers ($CD8^+$), T-helpers ($CD4^+$), B-lymphocytes ($CD19^+$), as well as natural killers (NK) and natural killer T-cells (NKT) in the experimental samples compared with the control ones (Tables 1, 2).

Activation of lymphocytes in response to interaction with a foreign agent, including a virus, is a well-known fact. However, at this stage, without additional studies, it is impossible to accurately determine the mechanisms underlying the ability of the RVK228 strain to maintain lymphocyte proliferation. However, there are a number of works that provide results similar to ours and investigate possible intermediary cells of the mitogenic activity of rotaviruses *in vitro*. So, in the work of Yasukawa et al. [12], it was suggested that the source of the mitogenic effect on the lymphocytes of the Wa strain of human rotavirus and the NCDC strain of cow rotavirus are memory T cells that previously came into contact with this group of viruses, since this effect was not observed in experiments with umbilical cord blood, whose lymphocytes were naive to pathogens. The repeated encounter with the virus, according to the authors, provoked the active proliferation of memory T cells and the production of such factors as interleukin-2 (IL-2) and interferon-γ (IFN-γ), which stimulate the proliferation of lymphocytes [12]. However, in more recent studies by other authors, it was shown that the primary source of activation of lymphocytes, including T cells, by rotaviruses are plasmacytoid dendritic cells (PDC) [13, 14], which are present in a small amount in all MNC preparations. Thus, in the work of Mesa et al. [13], it was shown that macs, when infected with the Wa strain, secrete proinflammatory cytokines IL-6, tumor necrosis factor-α (TNF-α) and IFN-α into the medium, which, in turn, leads to the activation of T-helpers and their production of regulatory cytokines IFN-γ, IL-2 and IL-10. In the same study, it was shown that in addition to PDC, monocytes and B cells are susceptible to rotavirus infection, with almost complete resistance of T cells to it, which is associated with α4-integrin and other unexplored factors [13]. It is emphasized that the infection is of a short-term nature and does not affect the viability of these cells, which is consistent with the results of our experiment.

Despite the fact that our study did not observe a relative increase in the number of T-helpers, which is mentioned in the study of Yasukawa et al. [12], we can assume that this subpopulation is activated, as evidenced by an increase in the proportion of $CD4^+CD38^+$ cells. Whether the activation of T-helpers is direct or mediated by antigen-presenting cells, as well as how much T-helpers are involved in maintaining the proliferative activity of MNCs, has yet to be established. Given that in our study we are studying the properties of a previously unexplored group of rotaviruses, the mechanism of their interaction with blood cells may differ from mechanisms given in the works cited above.

CONCLUSION

The studied strains of human rotaviruses belonging to group K, first described at the Rostov Institute of Microbiology and Parasitology, do not have cytotoxic activity against human lymphocytes *in vitro*. Moreover, the RVK228 strain probably has the ability to activate T cells, but further research is required to test this hypothesis.

Authors contribution:

Kit O.I. – scientific editing.

Filippova S.Yu. – analysis and interpretation of data, preparation of illustrations, writing the text of the article.

Timofeeva S.V. – conducting experiments with the isolation and cultivation of lymphocytes, setting up a colorimetric study, primary processing of the results.

Sitkovskaya A.O. – research design, technical editing.

Zlatnik E.Yu. – the concept of research and scientific editing.

Kolpakov S.A. – isolation and growth of RVK strains.

Kolpakova E.P. – isolation and growth of RVK strains.

Bondarenko E.S. – cytofluorimetric analysis.

Novikova I.A. – scientific editing.

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