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Роль растворимых молекул CD25, CD38, CD95 в формировании иммуносупрессии при цитомегаловирусной инфекции

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Резюме: *Введение*. Инфицирование цитомегаловирусом (ЦМВ), принадлежащим к бета-герпесвирусам, широко распространено в человеческой популяции и приближается у пожилых лиц к 100 %. Обычно инфекция протекает в латентной форме, но при развитии иммуносупрессии способна к реактивации. Механизмы реактивации до конца не изучены. *Целью* настоящей работы явилось исследование роли растворимых молекул CD25, CD38, CD95 в формировании иммуносупрессии при цитомегаловирусной инфекции. *Материалы и методы*. В работе использовали образцы сыворотки крови больных с цитомегаловирусной инфекцией в стадии реактивации, подтвержденной с помощью клинических и лабораторных данных. Больные проходили лечение в Инфекционной клинической больнице № 2 г. Нижнего Новгорода. Сывороточное содержание суммарных и олигомерных растворимых молекул CD25, CD38 и CD95 определяли иммуноферментным методом с помощью моноклональных антител и поликлональных антител, направленных против белков мононуклеарных клеток периферической крови человека. Результаты регистрировали спектрофотометрически и оценивали, переводя единицы оптической плотности в условные единицы (U/ml). *Результаты*. Показано, что у больных с реактивацией цитомегаловирусной инфекции происходит повышение сывороточного содержания суммарной и олигомерной фракций растворимых молекул CD25, CD38 и CD95. Если сывороточное содержание суммарной и олигомерной фракций молекул CD25 и CD38 повышается в одинаковой степени, то для олигомерной фракции молекул CD95 обнаружено более выраженное повышение в сравнении с суммарной фракцией. Полученные данные позволяют предположить наличие при цитомегаловирусной инфекции механизма супрессии иммунного ответа, связанного с инициацией апоптоза эффекторных Т-лимфоцитов с участием олигомерной формы молекул CD95. *Заключение*. Изменения в содержании и структурно-функциональном состоянии растворимых дифференцировочных молекул CD25, CD38 и CD95 свидетельствуют об их участии в механизмах иммуносупрессии у больных с цитомегаловирусной инфекцией.

Ключевые слова: цитомегаловирсная инфекция, иммуносупрессия, растворимые молекулы CD25, CD38, CD95.

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The Role of Soluble Molecules CD25, CD38, and CD95 in the Development of Immunosuppression in Cytomegalovirus Infection

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Summary. *Introduction*: Cytomegalovirus (CMV) infection is a common beta-herpesvirus infection widely spread in the human population. The proportion of infected population increases with age and approaches 100 % in elderly people. The infection is usually latent but is capable of reactivation when immunosuppression develops. The mechanisms of reactivation are not fully understood. The *objective* of our study was to evaluate the role of soluble molecules CD25, CD38, CD95 in the development of immunosuppression in CMV infection. *Materials and methods*: We used 18 serum samples from cases of CMV disease in the stage of reactivation, all confirmed by clinical and laboratory data. The patients received treatment in Nizhny Novgorod Infectious Disease Hospital No. 2. The serum content of the total and oligomeric soluble molecules CD25, CD38, and CD95 was identified by ELISA using monoclonal and polyclonal antibodies against human peripheral blood mononuclear cell proteins. The results were recorded spectrophotometrically and evaluated by converting optical density units to conventional units (U/mL). *Results*: We established an increase in the serum content of total and oligomeric fractions of soluble molecules CD25, CD38, and CD95 in the cases of CMV disease. While the serum content of the total and oligomeric fractions of molecules CD25 and CD38 increased equally, the oligomeric fraction of molecules CD95 demonstrated a more pronounced increase compared to the total fraction of these molecules. Our findings suggest the immune response suppression mechanism associated with initiation of apoptosis of effector T lymphocytes involving oligomeric form of molecules CD95. *Conclusion*: Changes in the content, structural and functional state of soluble differentiating molecules CD25, CD38, and CD95 indicate their involvement in immunosuppression mechanisms in patients with CMV infection.

Keywords: cytomegalovirus infection, immunosuppression, soluble molecules CD25, CD38, and CD95.
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Cytomegalovirus (CMV) infection is a common beta-herpesvirus infection widely spread in the human population. CMV is usually acquired in childhood through body fluids, such as saliva, tears, urine, breast milk, and other secretions from infected individuals, and can be also transmitted through organ and tissue transplants. The proportion of infected population increases with age and approaches 100 % in elderly people [1]. Pathogenic properties of CMV were first discovered in 1965, when it was shown to be associated with a disease similar to infectious mononucleosis [2]. At present, it is well known that CMV causes a wide range of clinical syndromes based on immunosuppression. Primary CMV infection is usually asymptomatic, although it can manifest itself as a nonspecific febrile illness or infectious mononucleosis-like syndrome characterized by fever and lymphadenopathy. The result is a latent infection of many cells, including endothelial, epithelial, smooth muscle cells and fibroblasts, where the virus can replicate and then be spread by peripheral monocytes and circulating endothelial cells throughout the body [3]. Primary CMV infection leads to the production of CMV-specific IgM and later IgG antibodies, which persist throughout life and act as markers of infection [4]. Reactivation of CMV infection is observed in immunocompromised persons, such as AIDS patients, recipients of solid organ transplants and hematopoietic stem cells, cancer patients on the background of immunosuppressive therapy, and newborns with intrauterine infection. CMV infection during pregnancy can lead to intrauterine infection of the fetus and congenital CMV disease. Reactivation of CMV infection is accompanied by certain changes in cellular immunity, particularly CD4+ lymphopenia, induced by the increased production of such cytokines as IL-1, gamma interferon, IL-21, and IL-17A, but a reduced production of IL-2 [5–9]. The reduced IL-2 level, the production by the virus itself of an IL-10-like protein causing immunosuppression, and an increase in the level of TGF-beta production hamper adequate immune response. One of the important signs of CMV infection is the presence of the population of CMV-specific CD8+ memory T cells, leading to a phenomenon called memory inflation, and indicating immunodeficiency. Molecular mechanisms of developing immunosuppression are still far from being fully understood [10].

The objective of our study was to evaluate the role of soluble molecules CD25, CD38, and CD95 in the formation of immunosuppression related to CMV infection.

Materials and methods. We used 18 serum samples from cases of CMV infection in the stage of reactivation, all confirmed by clinical and laboratory data. The patients received treatment in Nizhny Novgorod Infectious Disease Hospital No. 2. Healthy volunteers' serum samples were kindly provided by the Nizhny Novgorod Regional Blood Transfusion Center. The serum content of total and oligomeric soluble molecules CD25, CD38, and CD95 was determined using mouse monoclonal antibodies (MCA) of the ICO series (MCA ICO-105, ICO-20, and ICO-160, respectively) and goat polyclonal antibodies against human peripheral blood mononuclear cell proteins [11].

To determine the level of total fractions of soluble molecules, polyclonal antibodies were diluted with 0.85 % NaCl solution in the ratio of 1 : 700, 1 : 500, and 1 : 1,000 respectively. To determine the level of oligomeric fractions of soluble molecules CD25, CD38, and CD95, monoclonal antibodies ICO-105, ICO-20, and ICO-160, respectively, were used in dilution of 1 : 500, 1 : 700, and 1 : 1200. The antibodies were adsorbed to plates in a volume of 100 μg/mL. The plates were incubated for 2 hours at 42 °C and the unbound antibodies were then washed four times with phosphate saline buffer (pH 7.4) with 0.1 % Tween-20 (PSB-T). In the first well row of the adsorbed material, 100 μL of positive control serum was added in the following dilutions: whole serum, 1 : 2, 1 : 4, 1 : 8, 1 : 64, etc. Serum was diluted with PSB-T, 100 μL of PSB-T was added to 2 to 3 wells to control background reactions. The rest of the wells were filled with 100 μL of the studied serum samples. The tablets were incubated for 24 hours at room temperature and washed as described above. Then, 100 μL of a solution of monoclonal antibodies conjugated with horseradish peroxidase was added to all wells in the working concentration (ICO-105, ICO-20, and ICO-160 in dilution for the total forms of 1:500, 1 : 700, and 1 : 1,200, respectively, for oligomeric forms – 1 : 1,000). The plates were incubated during one hour at 42 °C and then washed 5 to 6 times with PSB -T. To manifest the reaction, 100 μL of the freshly prepared substrate solution was added to all the wells. The enzymatic reaction was stopped after 20 minutes by adding 50 μL of the stop reagent, and the microplates were immediately placed in a Multiskan® EX microplate photometer (Finland) for measurement at a wavelength of 450 nm. The instrument readings were then converted from optical density units to conventional units (U/mL).

The calibration curve was constructed on the basis of the positive control titration. The optical density

value corresponding to the working dilution of the studied serum samples was taken as 1,000 U/mL.

Statistical data processing was performed using the Mann-Whitney test. The results were calculated using the Biostatistics software.

Results. The serum level of the total fraction of soluble molecules CD25 was 193.2 ± 9.0 U/mL, which was statistically significant (p = 0.004) and 1.9 times higher than the norm (98.4 ± 9.0 U/mL). An even more pronounced 2.2-fold excess (P = 0.001) was observed for the oligomeric form of soluble molecules CD25 (Fig. 1).

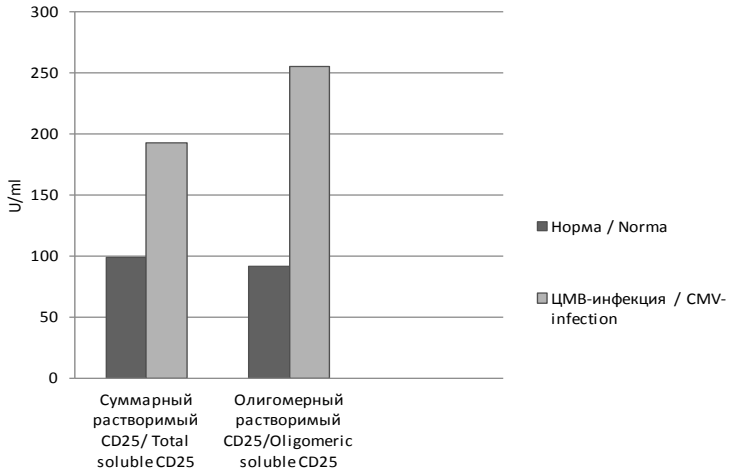
The increased level of soluble molecules CD25 (soluble interleukin-2 receptor, sIL-2R) reflects activation of T cells and appears in the blood due to proteolytic shedding from activated cells on the feedback principle, inhibiting the immune response [12]. One of the sources of soluble molecules CD25 is regulatory T cells characterized by a high density of expression of CD25 molecules [13]. By releasing large amounts of soluble CD25 molecules into the intercellular space, regulatory T cells can further control T cell proliferation, enhancing their inhibitory effect [14]. An increase in the serum level of the soluble interleukin-2 receptor was reported in patients with acute CMV mononucleosis syndrome and in women of childbearing age with CMV infection [15, 16]. An increase in the serum level of soluble molecules CD25 was shown during CMV reactivation after liver transplantation [17]. Recently, an increase in the serum content of the total fraction of soluble CD25 molecules in the blood of patients with CMV hepatitis was demonstrated [18]. However, the total fraction of these proteins is represented in the blood by both monomeric and oligomeric (dimeric) forms. The function of the latter remains unclear, but it is assumed to be involved in the development of immunosuppression [11]. Our findings show similar changes in the level of the oligomeric and total fraction of soluble molecules CD25, which indicates their joint participation in the inhibition of the immune response during CMV infection.

Another differentiating molecule that takes part in the activation of T cells in the membrane form and is capable of inhibiting immune reactions in a soluble form is the molecule CD38 [19, 20]. Changes in the serum content of its known dimeric (oligomeric) form in immunodeficiency states differ from the changes in the content of the total fraction of soluble molecules CD38 [21]. In our patients infected with CMV, the serum level of the total fraction of soluble molecules CD38 averaged 356.0 ± 61.7 U/mL, which was 1.8 times higher than the normal level (200.3 ± 16.5 U/mL, p = 0.006). The content of the oligomeric fraction changed similarly (Fig. 2).

The membrane form of molecules CD38 has several functions. Along with the transmission of a signal within the cell during activation of lymphocytes, it is able to act as an adhesion protein involved in intercellular interactions and cell migration. Soluble CD38 molecules in this situation can act as blockers of these processes causing immunosuppression typical of CMV infection in the activation stage.

The molecule that serves, on the one hand, as an activation antigen of lymphocytes, and, on the other hand, is a receptor initiating one of the pathways of external apoptosis (Fas-mediated apoptosis), is the CD95 molecule. In its soluble form, it has either pro-apoptotic or anti-apoptotic properties, depending on its structural state. It has been demonstrated that the oligomeric form of the soluble molecule CD95, interacting with the Fas ligand on the membrane of effector T lymphocytes, causes their apoptosis by reverse signaling. The monomeric form inhibits the apoptotic processes of target cells [22–24].

In our studies, the content of the total form of soluble molecules CD95 increased in the blood serum of patients with CMV infection by 1.4 times (p = 0.036) from 374.5 ± 23.0 U/mL in healthy volunteers to 533.0 ± 56.7 U/mL in the infected patients. For the oligomeric form of this protein molecule, more pronounced changes in its content were recorded. The serum level of the oligomeric form of CD95 increased in patients with CMV infection by 2.2 times (p = 0.001) (Fig. 3). An increase in the serum content of the



*p<0,05 различия значимы / the differences are significant

Рис. 1. . Сывороточный уровень суммарной и олигомерной фракций растворимых молекул CD25 в крови здоровых лиц и больных с цитомегаловирусной инфекцией
* – статистически значимые различия со здоровыми донорами крови (P < 0,05)

Fig. 1. . The serum level of the total and oligomeric fractions of soluble molecules CD25 in the blood of healthy persons and cases of CMV disease
* – statistically significant differences with healthy blood donors (P < 0.05)

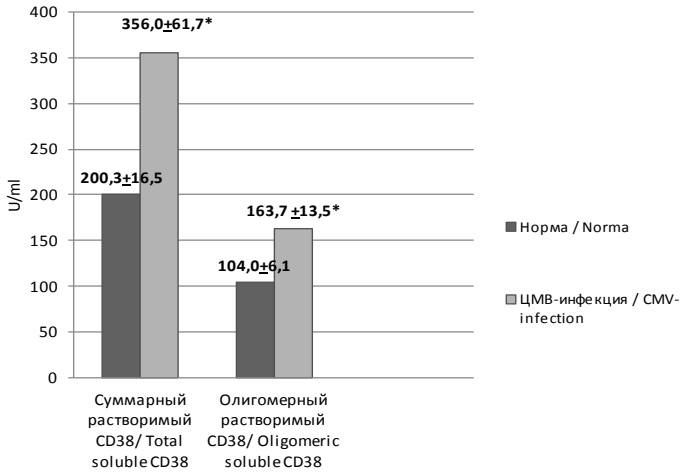
total fraction of soluble molecules CD95 in the blood of patients with acute CMV infection after liver transplantation was reported previously [25]. A more pronounced increase in the oligomeric fraction of soluble molecules CD95 in comparison with their total fraction observed in our study suggests the presence of a CMV infection-related mechanism for suppressing the immune response associated with the initiation of apoptosis of effector T lymphocytes. The apoptosis in this situation will be triggered by the interaction of oligomeric forms of soluble molecules CD95 with their membrane ligand on the cell surface (Fas ligand), followed by transmission of the death signal to the cells.

Thus, with the reactivation of CMV infection, pronounced disorders occur not only in the state of the cytokine network which controls the immune response, but also in the structural and functional state of the pool of soluble differentiating molecules such as CD25, CD38, and CD95. At the same time, not only the content of these proteins in the biological fluids of the body changes, but there occur shifts in their nanostructural state, e.g., the relative content of the oligomeric form of molecules CD95 increases in relation to the total fraction of these proteins. The detected shifts in the state of the pool of soluble differentiating molecules in patients with reactivated CMV infection contribute to the development of immunosuppression, inhibiting various mechanisms of T cell immunity.

Conclusions

1. An increase in the serum content of total and oligomeric fractions of soluble molecules CD25, CD38 and CD95 occurs in patients with reactivated CMV infection.

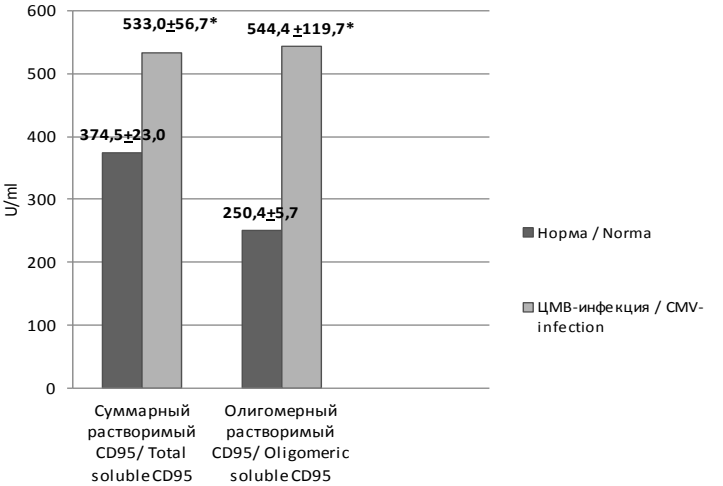
2. While the serum content of the total and oligomeric fractions of molecules CD25 and CD38 increased equally, the oligomeric fraction of



* p<0,05 различия значимы / the differences are significant

Рис. 2. Сывороточный уровень суммарной и олигомерной фракций растворимых молекул CD38 в крови здоровых лиц и больных с цитомегаловирусной инфекцией
* – статистически значимые различия со здоровыми донорами крови (P < 0,05)

Fig. 2. The serum level of the total and oligomeric fractions of soluble molecules CD38 in the blood of healthy persons and cases of CMV disease
* – statistically significant differences with healthy blood donors (P < 0.05)



* p < 0,05 различия значимы / the differences are significant

Рис. 3. Сывороточный уровень суммарной и олигомерной фракций растворимых молекул CD95 в крови здоровых лиц и больных с цитомегаловирусной инфекцией
* – статистически значимые различия со здоровыми донорами крови (P < 0,05)

Fig. 3. The serum level of the total and oligomeric fractions of soluble molecules CD95 in the blood of healthy persons and cases of CMV disease.
* – statistically significant differences with healthy blood donors (P < 0.05)

molecules CD95 demonstrated a more pronounced increase in comparison with the total fraction of these molecules.

3. Changes in the content, structural and functional state of soluble differentiating molecules CD25, CD38, and CD95 indicate their involvement in immunosuppression mechanisms in patients with CMV infection.

Author contribution: V.V. Novikov developed the study design; G.A. Kravchenko obtained and analyzed data; D.M. Sobchak analyzed clinical materials; D.V. Novikov obtained data and reviewed publications on the topic; S.V. Shumilova wrote the text of the manuscript.

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Respect for patients' rights: A written informed consent was obtained from all subjects prior to participation.

Compliance with the rules of bioethics: The study protocol was approved by the Ethics Committee of the Academician I.N. Blokhina Nizhny Novgorod Scientific Research Institute of Epidemiology and Microbiology.

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(пп. 1–10, 12–18, 21, 23–25 см. References)

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