ВЛИЯНИЕ ТРОФОБЛАСТИЧЕСКОГО β1-ГЛИКОПРОТЕИНА НА ДИФФЕРЕНЦИРОВКУ МИЕЛОИДНЫХ СУПРЕССОРНЫХ КЛЕТОК

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Резюме. Миелоидные супрессорные клетки (MDSC) – гетерогенная клеточная популяциия, угнетающая функции, преимущественно, Т-лимфоцитов при здоровой беременности и патологиях. MDSC считаются одними из ключевых регуляторов иммунных реакций, поиск способов управления которыми крайне актуален для терапии рака, аутоиммунных заболеваний, невынашивания беременности и посттрансплантационных осложнений. Механизмы иммуносупрессии MDSC связаны с экспрессией молекул CD73, ADAM17, PD-L1, продукцией аргиназы 1 (Arg 1), индуцибельной синтазы оксида азота (iNOS), индоламин-2,3-диоксигеназы (IDO) и цитокинов IL-10 и TGF-β1.

Трофобластический β1-гликопротеин (ТБГ) – гликопротеин беременности. Описаны его модулирующие эффекты в отношении дендритных клеток и макрофагов, опосредующие сдвиг фенотипов Т-клеток в сторону Th2 и Treg. Ранее нами было показано что нативный ТБГ подавляет дифференцировку Th17 и продукцию ими провоспалительных цитокинов. Кроме того, этот гликопротеин стимулировал продукцию IDO моноцитами и дифференцировку Treg.

Так как функции и специфичность нативных и рекомбинантных белков отличаются, а рекомбинантные белки более доступны и перспективны, необходимо исследовать оба вида препаратов.

Учитывая иммуномодулирующие свойства ТБГ, а также ключевую роль MDSC в патологиях, целью нашей работы стала оценка влияния нативного и рекомбинантного ТБГ на дифференцировку MDSC *in vitro*.

MDSC дифференцировали из $CD11b^+$ клеток периферической крови. Клетки культивировали 7 дней, поэтапно добавляя GM-CSF, IL-1β и LPS. Нативный (н) (1,10 и 100 мкг/мл) и рекомбинантный (р) (1 и 10 мкг/мл) ТБГ вносили в культуры за три дня до окончания инкубации. Методом проточной цитометрии определяли процент MDSC ($Lin^-HLA\text{-}DR^-CD11b^+CD33^+$) от клеток в культуре, а также проценты M- ($Lin^-HLA\text{-}DR^-CD11b^+CD33^+CD14^+CD66b^-$), PMN- ($Lin^-HLA\text{-}DR^-CD11b^+CD33^+CD14^-CD66b^+$) и e-MDSC ($Lin^-HLA\text{-}DR^-CD11b^+CD33^+CD14^-CD66b^-$) от общего количества MDSC.

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Обнаружено, что нТБГ не влиял на процент MDSC в культурах. Однако рТБГ (1 мкг/мл) увеличивал процент этих клеток по сравнению с контролем. нТБГ (1 и 10 мкг/мл) и рТБГ (10 мкг/мл) увеличивали процент M-MDSC. Кроме того, рТБГ (10 мкг/мл) угнетал дифференцировку $CD11b^+$ клеток в PMN-MDSC. Процент e-MDSC под действием ТБГ не изменялся.

Можно сделать вывод, что цитокиновый фон в культурах $CD11b^+$клеток способствовал дифференцировке преимущественно M-MDSC, сходно с опухолевым микроокружением, а нативный и рекомбинантный ТБГ усиливали этот эффект.

Таким образом, нТБГ и рТБГ обладают способностью модулировать дифференцировку MDSC, увеличивая их количество, преимущественно за счет моноцитарной субпопуляции. Этот факт открывает перспективы для новых исследований, касающихся направленного манипулирования клетками MDSC с целью применения клеточных технологий в науке и медицине.

Ключевые слова: миелоидные супрессоры, иммуносупрессия, трофобластический β1-гликопротеин, моноцитарные миелоидные супрессоры, гранулоцитарные миелоидные супрессоры, $CD11b^+CD33^+$ клетки

EFFECT OF PREGNANCY-SPECIFIC β1-GLYCOPROTEIN ON MYELOID-DERIVED SUPPRESSOR CELL DIFFERENTIATION

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Abstract. Myeloid-derived suppressor cells (MDSCs) are a heterogeneous cell population that primarily suppress T lymphocytes in healthy pregnancies and pathologies. MDSCs are one of the key regulators of immune responses. Finding ways to control them is important for the treatment of cancer, autoimmune diseases, miscarriage, and post-transplant complications. The mechanisms of immune suppression by MDSC are: expression of CD73, ADAM17, PD -L1, production of Arg 1, iNOS, IDO, IL -10 and TGF-β1.

Pregnancy-specific β1-glycoprotein (PSG) has modulatory effects on dendritic cells and macrophages that mediate the shift of T cell phenotypes toward Th2 and Treg. We have previously shown that native PSG suppresses Th17 differentiation and cytokine production, stimulates the production of IDO by monocytes and the differentiation of Tregs.

Considering the immunomodulatory properties of PSG and the key role of MDSCs in pathologies, the aim of our work was to investigate the effect of native and recombinant PSG on the differentiation of MDSCs *in vitro*.

MDSCs were differentiated from $CD11b^+$ peripheral blood cells. Cells were cultured for 7 days and received stepwise GM-CSF, IL-1β, and LPS. Native (n) (1; 10 and 100 μg/mL) and recombinant (r) (1 and 10 μg/mL) PSG were introduced into the cultures three days before the end of incubation. Flow cytometry was used to determine the percentage of MDSC among the cells in culture and the percentage of M-, PMN-, and e-MDSC among the total number of MDSCs.

It was found that rPSG (1 μg/mL) increased the percentage of MDSCs in culture. Both nPSG (1 and 10 μg/mL) and rPSG (10 μg/mL) increased the proportion of M-MDSC, whereas rPSG (10 μg/mL) decreased the number of PMN-MDSC.

Thus, the cytokine background in $CD11b^+$ cell cultures favored the differentiation of predominantly M-MDSC, similar to the tumor microenvironment, whereas native and recombinant PSG enhanced this effect.

Thus, nPSG and rPSG are able to modulate the differentiation of MDSCs by increasing their number, mainly due to the monocytic subpopulation. This fact opens perspectives for new research on targeted manipulation of MDSCs.

Keywords: myeloid-derived suppressor cells, immunosuppression, pregnancy-specific β1-glycoprotein, $CD11b^+CD33^+$ cells, M-MDSC, PMN-MDSC

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Introduction

Myeloid-derived suppressor cells (MDSCs) are a small (usually less than 1% in blood) heterogeneous population composed of immature neutrophils and monocytes capable of suppressing innate and acquired immune responses, including those against tumors [3]. The number of MDSCs increases in healthy pregnancy [8] and in many pathological conditions, including inflammation, sepsis, traumatic shock, autoimmune diseases, and cancer [15].

The main mechanisms of immunosuppressive activity of MDSC are associated with the expression of a number of surface markers (CD73, ADAM17, PD-L1), intracellular expression of arginase 1 (Arg 1), iNO synthase (inducible nitric oxide synthase, iNOS), indoleamine 2,3-dioxygenase (IDO) and production of a number of cytokines (IL-10, TGF-β1) [1]. Due to the large arsenal of suppressive mechanisms, MDSCs are currently considered one of the most important regulators of immune responses. Finding ways to control them is extremely relevant from the perspective of therapy of all diseases and conditions in which these cells are involved. In addition, MDSCs may become a successful pharmacological target for solving problems related to immune rejection of both semi-allogeneic embryos and transplanted organs or tissues.

One of the factors that provide immune tolerance during pregnancy is pregnancy-associated proteins. Pregnancy-specific β1-glycoprotein (PSG) is a dominant fetoplacental protein produced by cyto- and syncytiotrophoblast cells and has immunoregulatory properties. In humans, the dominant expression product is PSG-1, which was discovered and identified in 1970 by a group of Russian researchers [11]. In pregnancy dynamics, the level of PSG gradually increases, reaching of 200-400 μg/mL in the third trimester, while its level in fetal blood serum does not exceed 1-2 μg/L [4]. It is known that PSG level in blood serum decreases in spontaneous abortion, ectopic pregnancy, intrauterine growth retardation, preeclampsia and fetal hypoxia [5]. In 2020, it was confirmed that circulating levels of PSG (PSG1) were significantly reduced in women with preeclampsia compared to healthy pregnant women. Thus, this protein is extremely important for the successful development of pregnancy.

The complex structure and multiple forms of PSG lead to certain difficulties in obtaining its pure, native active ingredient. Only recombinant forms of PSG are available for research, which have their drawbacks (structural differences, incomplete folding, uneven post-translational modification, etc.). Our team of authors has its own patented method for obtaining a native human PSG preparation [10], which ensures priority in research. Thus, in the last 5 years, we have demonstrated the effects of a native human PSG preparation obtained by the authors' method in terms of expression of IDO by antigen-presenting cells, regulatory T lymphocytes, Th17 cells, immune memory T cells, as well as regulation of the cytokine profile of these cells [13]. At the same time, it is obvious that for the practical application of the drug, it is necessary to study the recombinant forms of PSG in detail. The key point of our work is the fact that the role of PSG in regulating the differentiation and functional activity of MDSC has not yet been investigated.

Therefore, **the aim of this work** is to investigate the role of native and recombinant PSG in the regulation of MDSC differentiation in human peripheral blood.

Materials and methods

Peripheral blood from volunteer donors was collected by venipuncture (n = 4). The study was conducted in accordance with the WMA Declaration of Helsinki 2000 and the Protocol of the Council of Europe Convention on Human Rights and Biomedicine 1999; approval of the Ethics Committee of the IEGM Ural Branch of the Russian Academy of Sciences (IRB00010009) dated 15 February 2022 was obtained for the experimental scheme used. Written informed consent was obtained from all patients. The authors adhered to all relevant ethical standards.

Peripheral blood mononuclear cells (PBMC) were isolated by density gradient centrifugation (ρ = 1.077 g/cm^3, Diakoll, Dia-M, Russia). CD11b$^+$ cells were isolated from PBMC by positive immunomagnetic separation (MACSiBeads™, LS columns, (MiltenyiBiotec, Germany)). The resulting cells at a concentration of 1×10^6 were plated into a 96-well plate containing complete culture medium (RPMI-1640, 10% FBS, 10 mM Hepes (ICN Ph., USA), 2 mM-Glutamine (ICN Ph.) and 100 μg/mL penicillin-streptomycin-amphotericin (100 μL per 10 mL medium, BI, Israel)). GM-CSF (MiltenyiBiotec, Germany) was added to the cultures at a concentration of 20 ng/mL. Cells were then incubated for three days in a humidified atmosphere in a CO_2 incubator at 5% CO_2 and 37 °C. After completion of the first phase, the culture medium was replaced by addition of the cytokine IL -1β (20 ng/mL, MiltenyiBiotec, Germany) and LPS (0.1 μg/mL, Sigma Aldrich, USA) to activate the cells. The next day, the studied proteins were added: native PSG (RF Patent No. 2367449,

Raev M.B.) at concentrations of 1, 10, and 100 μg/mL and recombinant PSG (recombinant E. Coli-derived human pregnancy-specific beta-1-glycoprotein 1, PSG 1, Cusabio, China) at concentrations of 1 and 10 μg/mL. The choice of concentrations was based on their correspondence to the different trimesters of pregnancy. Cells were then cultured for an additional three days. After a total of 7 days of incubation, the cells were transferred to test tubes for flow cytometry. The cells were removed from the plate using a reagent containing enzymes that enhance cell detachment from the plastic (Accutase®, Capricorn Scientific, Germany), and the wells were additionally washed with ice-cold DPBS (Thermo Fisher Scientific, USA). Cells were then stained for viability with Zombie Aqua dye (BioLegend, USA) according to the manufacturer's protocol. After washing, the cells were incubated with fluorochrome-labeled antibodies to determine the MDSC phenotype using a flow cytometer. The following group of antibodies was used for this purpose: anti HLA-DR-Alexa Fluor 750, anti CD33-APC, anti CD11b-Alexa Fluor 405, anti CD66b-PE, anti CD14-PerCP (R&D Systems, USA). To exclude the presence of lymphocytes and NK cells in the target gate, three types of antibodies with the same fluorescent labeling were used: anti CD19-AF700, anti CD56-AF700, anti CD3-AF700 (designated as Lin). FMO samples (fluorescence minus one) and isotype controls were used as controls to determine negative populations.

Samples were then analyzed using a CytoFLEX S flow cytometer (Beckman Coulter, USA). Cells were first gated on a dot plot of side scatter (SSC) and forward scatter (FSC), then live cells that were not stained with Zombie Aqua dye were gated. Next, a region of $Lin^-HLA\text{-}DR$ cells was selected in the live cell gate and then plotted on a two-parameter CD11b/CD33 plot. The live $Lin^-HLA\text{-}DR^-CD33^+CD11b^+$ cells thus gated were plotted on a two-parameter CD14 and CD66b dot plot to determine M- (monocytic), PMN- (polymorphonuclear), and e-MDSC ("early," $Lin^-HLA\text{-}DR^-CD33^+CD11b^+CD14^-CD66b^-$) MDSC subpopulations, respectively.

Flow cytometry data were processed using CytExpert software (Beckman Coulter, USA).

Statistical data processing was performed with GraphPad Prizm 8.0.1 software using the Friedman test and Dunn post hoc test for multiple comparisons. Results are presented as median, lower quartile, and upper quartile: Me ($Q_{0.25}$-$Q_{0.75}$). The significance level was set at 0.05.

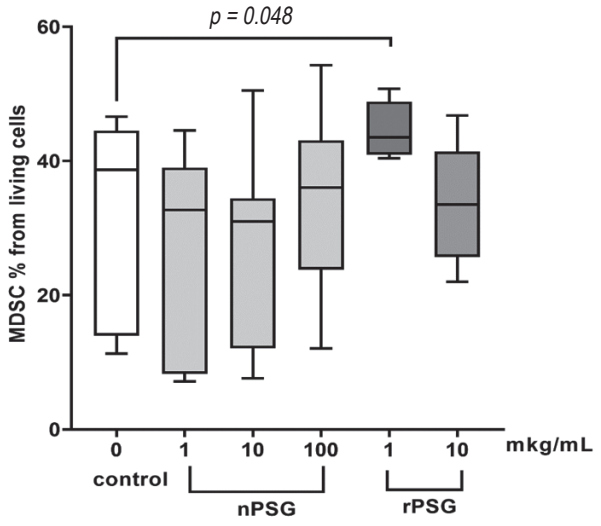

Figure 1. Effect of native (nPSG) and recombinant (rPSG) PSG on the percentage of MDSC in $CD11b^+$ cell cultures

Note. n = 4; x-axis is the type and concentration of PSG; y-axis is the percentage of MDSC in the live cell gate. Medians (horizontal lines), interquartile ranges (rectangles), maximum and minimum values ("whiskers") are shown. Significant differences ($p < 0.05$) compared with control are indicated.

Results and discussion

Viability in cultures of CD11b cells ranged from 95-98%. No statistically significant changes were observed.

Regarding the effects of the study proteins, it was found that the native PSG preparation did not affect the percentage of MDSC in the live cell gate. However, the recombinant protein preparation at a concentration of 1 μg/mL increased the percentage of these cells compared with the control (Figure 1).

The next task of our study was to determine the effects of native and recombinant PSG on the composition of MDSC subpopulations. To this end, we analyzed the percentage of $CD14^+$M-MDSC, $CD66b^+$ PMN-MDSC, and $CD14^-CD66b^-$e-MDSC in the total $CD11b^+CD33^+$ MDSC subset.

Native PSG at concentrations of 1 and 10 μg/mL and recombinant PSG at a concentration of 10 μg/mL were found to increase the percentage of M-MDSC (Figure 2).

Interestingly, recombinant PSG had a suppressive effect on the differentiation of $CD11b^+$ cells into CD $66b^+$ PMN-MDSC and reduced the proportion of these cells to as low as 0% in some cultures (Figure 3).

The native glycoprotein had no pronounced effect on the differentiation of this subpopulation.

Native and recombinant PSG did not alter the percentage of e-MDSC in CD11b cell cultures (data not shown).

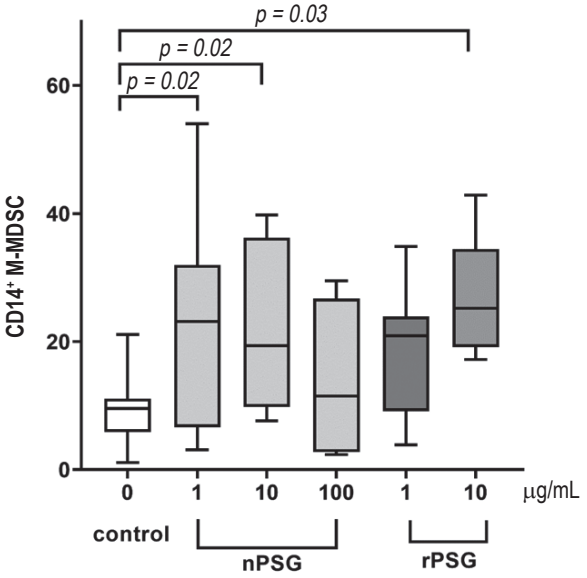

Figure 2. Effect of native (nPSG) and recombinant (rPSG) PSG on the percentage of CD14⁺ M-MDSC in CD11b⁺ cell cultures

Note. n = 4; x-axis is the type and concentration of PSG; y-axis is the percentage of CD14⁺M-MDSC in the MDSC gate. Medians (horizontal lines), interquartile ranges (rectangles), maximum and minimum values ("whiskers") are shown. Significant differences ($p < 0.05$) compared with control are indicated.

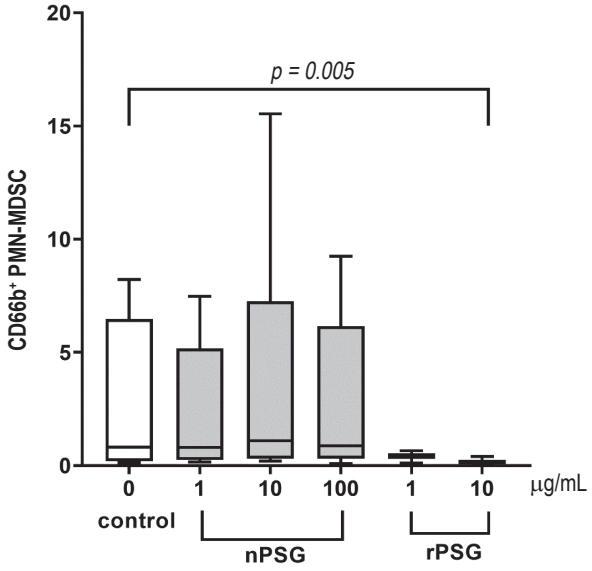

Figure 3. Effect of native (nPSG) and recombinant (rPSG) PSG on the percentage of CD66b⁺ PMN-MDSC in CD11b⁺ cell cultures

Note. n = 4; x-axis is type and concentration of PSG; y-axis is percentage of CD66b⁺ PMN-MDSC in MDSC gate. Medians (horizontal lines), interquartile ranges (rectangles), maximum and minimum values ("whiskers") are shown. Significant differences ($p < 0.05$) compared with control are indicated.

Thus, recombinant PSG at a concentration of 1 μg/mL was shown to increase the percentage of MDSC in CD11b⁺ cell cultures. This effect may be due to the fact that MDSCs exert a fetoprotective function during pregnancy by suppressing the maternal immune response to paternal antigens [15].

A specific receptor for PSG has not yet been found on human cells. However, it has been shown that PSG1 can exert its immunoregulatory functions by activating latent TGF-β1 and TGF-β2 [2]. TGF-β is considered one of the factors contributing to tumor progression and can "collaborate" with MDSCs from the tumor microenvironment [7]. Cells that cease to suppress T lymphocytes and acquire enhanced antigen-presenting and costimulatory capabilities. In addition, cells derived in this manner have acquired antitumor activity, which is very promising in terms of developing cell therapy against cancer [6].

The differences in the effects of native and recombinant proteins may be due to various factors. It should be emphasized that the native PSG preparation contains some quantity of PSG3, PSG7, PSG9 and some of their isoforms and precursors in addition to PSG1, whereas the recombinant protein contains only the PSG1. Moreover, the main difference between native proteins is their glycosylation, which determines their structure, functions, and stability, as well as the specificity of their interactions with the receptor.

As mentioned earlier, the distinguishing feature of MDSCs is their heterogeneity. The names of the main MDSC subpopulations, monocytic (M) and polymorphonuclear (PMN), are based on the morphological similarity of these cells to monocytes and neutrophils, which is also supported by the expression of the corresponding surface molecules CD14 and CD15/CD66b. In addition, PMN-MDSCs, whose major suppressive mechanism is the production of ROS, are known to require close intercellular contact with T cells, whereas M-MDSCs, which increase NO, arginase, and suppressive cytokines, do not require direct contact to suppress the T cell response. with cells. In addition, there is evidence that M-MDSCs are more effective per cell than PMN-MDSCs. Another difference is that in most tumor models, PMN-MDSCs accumulate in peripheral lymphoid organs, whereas M-MDSCs, in contrast, predominate directly in the tumor site. Presumably, hypoxia, low pH and other tumor microenvironmental factors do not support survival PMN-MDSC [15]. Interestingly,

PMN-MDSC predominates in decidua and blood during pregnancy [9].

In our study, both types of PSG (1 μg/mL nPSG and 10 μg/mL nPSG and rPSG) increased the percentage of M-MDSC in the general MDSC population, and recombinant PSG at a concentration of 10 μg/mL significantly inhibited the formation of PMN-MDSC. It should be noted that in our experiment, the ratio between the number of M-MDSCs and the number of PMN-MDSCs indicated a strong predominance of the former over the latter. In the cultures that served as controls, the number of M-MDSCs was 60-fold greater than that of PMN-MDSCs, and when both types of PSG were added, this number increased to 200.

This suggests that the cytokine background in the CD11b cell cultures promotes differentiation of predominantly M-MDSCs, similar to the tumor microenvironment, rather than PMN-MDSCs, as in the decidual membrane. Native and recombinant PSG likely enhanced this effect through TGF-β.

Conclusion

Thus, recombinant and native PSG have the ability to modulate the differentiation of MDSCs by increasing their number, which is mainly due to the monocytic subpopulation of these cells. This fact opens the prospect of new research on targeted manipulation of MDSCs with the aim of applying these technologies in science and medicine.

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