ASSESSMENT OF THE FEATURES OF INNATE LYMPHOID CELLS IN PATIENTS WITH MULTIPLE MYELOMA

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Multiple myeloma (MM) is a B-cell malignant tumor, the morphological substrate of which are plasma cells that produce monoclonal immunoglobulin. This is one of the most common tumors of lymphoid origin. It is known that during oncogenesis, the immune balance shifts towards suppression of the antitumor immune response. Innate lymphoid cells (ILC) are one of the key factors influencing the said balance. This study aimed to assess the features of ILC in MM patients. The peripheral blood levels of ILC1, ILC2, and ILC3, as well as the expression of HLA-DR on ILC 2, were measured with the help of flow cytometry. We found that MM patients (n = 14; 7 male and 7 female, mean age 59.2 ± 2.08) had significantly more ILC2 in the peripheral blood, with the content thereof amounting to 63.1 ± 4.51% among "helper" ILC, while in donors the proportion of ILC2 was 43.2 ± 6.17% (p = 0.03). MM patients were also found to have a decreased amount of ILC2 that express HLA-DR: the proportion of such cells was only 2.2 ± 1.53%, compared to 15.6 ± 5.29% in donors (p = 0.003). The results of this study point to the shift in the immune balance and polarization of the immune response towards type 2 (T2), which may contribute to the suppression of the antitumor immune response.

Keywords: innate lymphoid cells, antigen presentation, immune balance, multiple myeloma

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Compliance with ethical standards: the study was approved by the Ethics Committee of the Research Institute of Fundamental and Clinical Immunology (Minutes #145 of April 19, 2024). All participants signed the voluntary informed consent form.

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ОЦЕНКА ОСОБЕННОСТЕЙ ВРОЖДЕННЫХ ЛИМФОИДНЫХ КЛЕТОК У ПАЦИЕНТОВ С МНОЖЕСТВЕННОЙ МИЕЛОМОЙ

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Множественная миелома (ММ) — В-клеточная злокачественная опухоль, морфологическим субстратом которой являются плазматические клетки, продуцирующие моноклональный иммуноглобулин. Это одна из часто встречающихся опухолей лимфоидного происхождения. Известно, что в процессе онкогенеза происходит изменение иммунного баланса в сторону супрессии противоопухолевого иммунного ответа. Одними из ключевых факторов, влияющих на баланс параметров иммунной системы, являются врожденные лимфоидные клетки (innate lymphoid cells, ILC). Целью исследования было провести оценку особенностей врожденных лимфоидных клеток у пациентов с ММ. Оценку содержания в периферической крови ILC1, ILC2 и ILC3, а также экспрессии HLA-DR на ILC2 проводили методом проточной цитометрии. Обнаружено, что в периферической крови у пациентов (n = 14; 7 мужчин и 7 женщин, средний возраст 59,2 ± 2,08) с ММ доля ILC2 существенно выше и составляет 63,1±4,51% среди «хелперных» ILC, тогда как у доноров доля ILC2 43,2 ± 6,17% (p = 0,03). Выявлено, что у пациентов с ММ снижено относительное количество ILC2, экспрессирующих HLA-DR: доля этих клеток составила всего 2,2 ± 1,53% по сравнению с 15,6 ± 5,29% у доноров (p = 0,003). Полученные результаты свидетельствуют об изменении иммунного баланса и поляризации иммунного ответа в сторону иммунного ответа 2-го типа (Т2), что может способствовать супрессии противоопухолевого иммунного ответа.

Ключевые слова: врожденные лимфоидные клетки, презентация антигена, иммунный баланс, множественная миелома

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It is known that there are three main types of immune response [1]: T1, T2, and T17, which are regulated by T helper (Th) populations Th1, Th2, and Th17, respectively. The immune system is balanced between possible types of immune response [2]. Under the influence of a number of external and internal factors, this state, the immune equilibrium, changes over the person's lifetime in terms of the proportions of various types of immune responses [3-5]. In addition to the Th, innate lymphoid cells (ILC) are capable of influencing the immune balance. They can synthesize cytokines characteristic of Th much faster and in greater quantities, and thus either enhance or suppress the immune response at the earliest stages of its development [6].

By the ability to produce cytokines characteristic of the T1, T2, and T17 immune responses, ILC 1, ILC 2, and ILC3, respectively, are distinguished. However, it is currently believed that, in addition to acting similarly to T helper cells, ILCs form a link between the environment monitoring sensory cells (track all changes, not necessarily pathogenic) and effector cells, which translates into the support of body's homeostasis and immune balance [7]. Several mice studies demonstrated the MHC-dependent (major histocompatibility complex) cross-interaction of ILC-T cells [8–12], but the antigen-presenting properties of human ILC are still poorly understood. It has been shown that human intestinal tumor tissues contain ILCs that actively express HLA-DR, and most ILCs lack additional signaling molecules T cells stimulation. Together with T cells, HLA-DR$^+$CD127$^+$ phenotype ILC cells localize in the unaffected colon tissue and by the edge of the tumor, which indicates the possibility of physical interaction between these two types of cells. Earlier, ILCs were shown to suppress T cell response to intestinal commensal bacteria in mesenteric lymph nodes in mice [10, 11]. Therefore, presentation of ILC antigen in a complex with MHC class II without costimulatory signals may play a role in the development of immunosuppression while protecting the tumor from destruction by cells of the immune system. However, in the case of ILC2, the antigen presentation process may be significantly different. It has been shown that in addition to the production of T2 cytokines, ILC2 express MHCII in combination with costimulating molecules CD80, CD86, and the OX40L ligand. Thus, ILC2 can act as antigen-presenting cells (APC), processing and presenting antigens to T cells, thereby inducing the antigen-specific response of CD4$^+$T cells [13, 14].

In an oncopathology, an immune imbalance is one of the key factors triggering its development: T1 cytokines are associated with the increased antitumor immune response, whereas T2 cytokines can promote tumor growth and metastasis [15, 16]. In case of solid tumors of non-hematopoietic origins, cytokines are primarily a means of achieving immunosuppression of the antitumor response, but in hemoblastosis cases they can act as growth factors for tumor cells. In patients with chronic lymphocytic leukemia, characterized by the production of atypical mature B lymphocytes, a shift towards Th2 was noted, which is corrected by ibrutinib (Bruton's tyrosine kinase inhibitors) [17].

In the case of multiple myeloma (MM), the number of CD4$^+$-Th1 and CD4$^+$-Th17 in patients was higher than in donors [18]. However, despite the greater numbers in this cell population, the concentration of T2 cytokine IL4 (interleukin-4) was significantly increased in the blood serum. Therefore, the high production of this cytokine may be primarily associated with its secretion by the ILC2 cells.

The purpose of this study is to evaluate the features of innate lymphoid cells in patients with MM.

METHODS

The study included 14 MM patients and 13 conditionally healthy donors. Both study groups were comparable in terms of gender and age characteristics. The study was conducted from May to November 2024. Test group inclusion criteria: MM diagnosis, any sex, age 18–65 years; II and III clinical stages (Durie-Salmon Staging System); complete remission (CR) or very good partial remission (VGPR) at the moment of inclusion; written informed consent. Control group inclusion criteria: good health, any sex, age 18–65 years; no autoimmune, oncological and chronic recurrent viral infections.

Exclusion criteria (both groups): non-compliance with the inclusion criteria; severe decompensated cardiovascular, respiratory, and liver failure; acute infectious diseases; pregnancy; mental disorders; refusal of the patient or donor to participate in the study.

Peripheral blood mononuclear cells (PBMC) were the studied material; it was isolated in the volume of 30–50 ml from the samples taken in both groups by standard Ficoll-Urografin density gradient centrifugation.

To determine the immunophenotype of the ILC, the isolated PBMC were stained with monoclonal antibodies conjugated with fluorochromes: anti-Lineage (CD2/3/14/16/19/20/56/235a), antiCD11c and anti-FceR1 alpha-FITC, anti-CD294-PE, anti-CD127-PerCP/Cy5.5, anti-CD117-APC, HLA-DR-PE/Cy7. The total number of ILC was established as Lin–CD127$^+$, since these cells do not carry linear markers, but have an alpha chain of the IL7 receptor on their surface. To assess the ratio of different ILC subpopulations, we counted CD294$^+$ILC (ILC2); CD117–CD294–ILC was taken as ILC1, and CD117$^+$CD294–ILC as ILC3. The cell phenotype was established using a LongCyte flow cytometer (Challenger, China).

Statistical processing of the results was performed using GraphPadPrizm 9.0.0 (GraphPad Software, Inc., USA). The Mann–Whitney test was used to compare the values registered in the groups. The results are presented as a median (Me) with interquartile range [25th; 75th percentile]. The results were considered significant at $p < 0.05$.

RESULTS

We have established that MM patients have a lower relative amount of peripheral blood "helper" ILC compared to the conditionally healthy individuals: 0.05% [0.03; 0.16] versus 0.24% [0.06; 0.48] (Fig. 1). It should be noted that the smaller total number of ILC is the result of erosion of the subpopulation composition of these cells. The relative amount of ILC2 in PBMC was 0.06% [0.02; 0.17] and 0.04% [0.02; 0.09], healthy donors and MM patients, respectively, the difference being insignificant (Fig. 2). In healthy donors, the predominant type was ILC1, the proportion of which in the peripheral blood was 0.07% [0.02; 0.19], while that of ILC3 amounted to 0.008% [0.003; 0.018]; in MM patients, the relative amounts of ILC1 (Fig. 3) and ILC3 (Fig. 4) were 0,02% [0,01; 0,04] and 0.001% [0; 0.004], respectively, which is significantly lower than in the control group.

Naturally, such changes altered the balance of different ILC populations. Assessing the proportion of ILC2 in MM patients, we noticed that it was greater than in the control group (Fig. 5).

We have also investigated the expression of HLA-DR (one of the MHC class II antigens needed for antigen presentation) on the surface of ILC2, and found that MM patients had significantly fewer ILC2 expressing the HLA-DR antigen on their membrane than healthy donors (Fig. 6). Consequently,

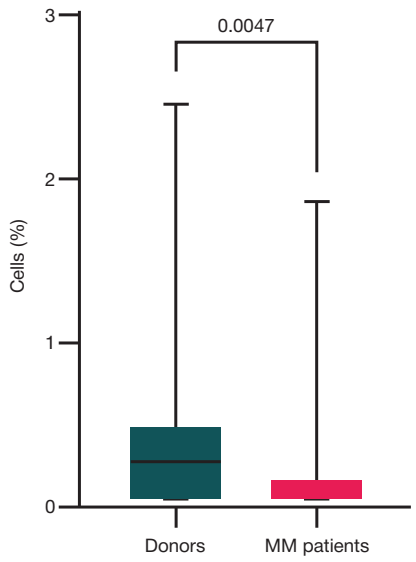

Fig. 1. The relative amount of ILC in the total PB MNC, MM patients and conditionally healthy individuals

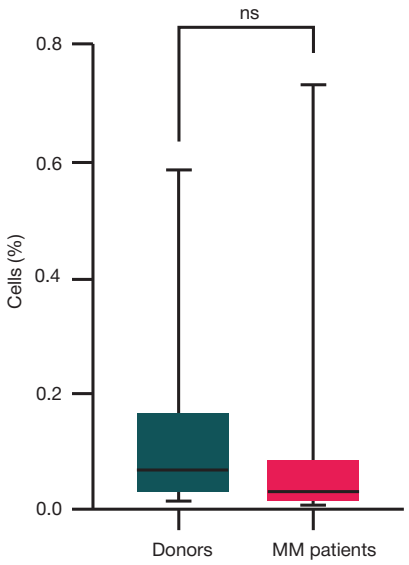

Fig. 2. The relative amount of ILC2 in the total PB MNC, MM patients and conditionally healthy individuals

despite the increased relative amount of ILC2 in MM patients, the ability of cells to present the antigen in this disease is hampered, which can weaken the antitumor immune response and decrease activation of T-lymphocytes.

DISCUSSION

According to the literature, there may be several specific features of functioning of ILC in hematologic cancers, which were demonstrated for acute myeloid leukemia and chronic lymphocytic leukemia [19]. Firstly, in such cases, the amount of ILC is smaller, and their functional activity weaker, which translates into a lower concentration of cytokines in the tumor microenvironment, and, as a result, suppression of the immune response. Secondly, activation of ILC 2 and polarization of the immune response towards T2 can boost the activity of suppressor cells. Thirdly, outside the tumor, in normal tissues, ILC maintain homeostasis and participate in tissue repair, including in the context of a graft-versus-host reaction, which is a common complication after allogeneic stem cell transplantation.

In this study, we found that in MM patients, despite the decreased relative content of "helper" ILC in PBMC, the ILC2 subpopulation count remained similar to that registered in healthy individuals. Consequently, such changes could have broken the ILC subpopulations balance, triggered growth of the proportion of ILC2 and direct the immune response towards T2, as well as cause the drop in the number of ILC1 that support the T1 type of immune response, which is most effective against tumor cells. It is known that polarization of the immune response towards T2 and weakening of the T1 immune response promote inactivation of anti-tumor immunity and thus boost tumor growth, a situation often observed in malignant neoplasm cases.

It should also be noted that our results are consistent with the reported growth of the level of T2 cytokines in MM patients [18]. In addition, with monoclonal gammopathy of undetermined significance (MGUS) in the background, which precedes MM, the peripheral blood level of ILC2 is increased [20]. Bone marrow level of ILC1 is known to grow MGUS cases, but the functional activity of ILC1 and ILC2 determined by the intracellular cytokine content goes down. In our study, MM also

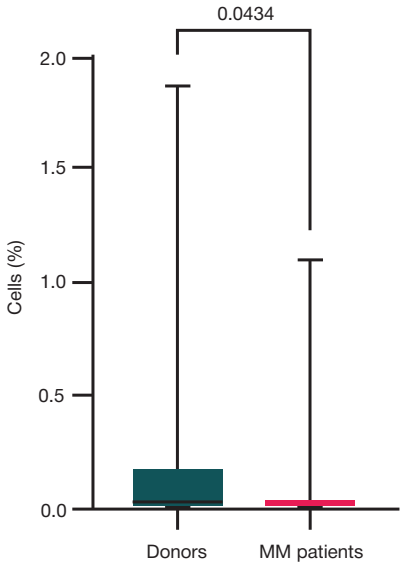

Fig. 3. The relative amount of ILC1 in the total PB MNC, MM patients and conditionally healthy individuals

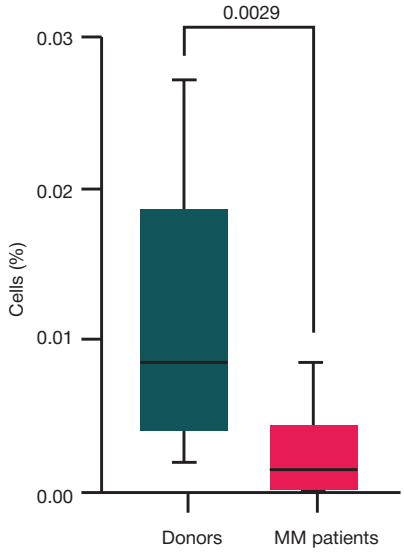

Fig. 4. The relative amount of ILC3 in the total PB MNC, MM patients and conditionally healthy individuals

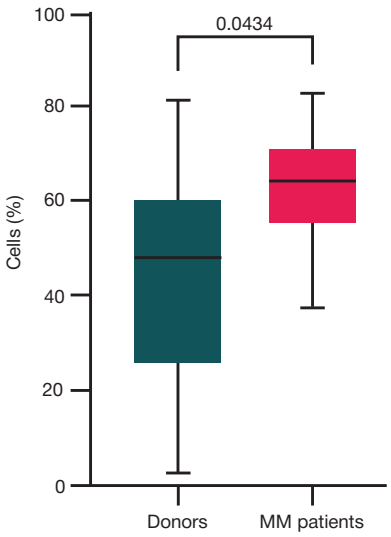

Fig. 5. The relative amount of ILC2 in the total number of ILC, MM patients and conditionally healthy individuals

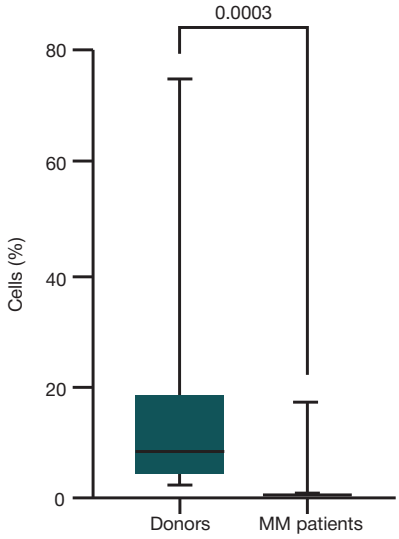

Fig. 6. The relative amount of HLA-DR+ILLC2 in the total number of ILC2, MM patients and conditionally healthy individuals

triggered a drop of the share of ILC2 cells capable of presenting the antigen. Other authors have demonstrated a decrease in the proportion of ILC2 among peripheral blood Lin–CD127⁺ cells [21], which may be due to differences between patient groups, since this study included patients with a fresh diagnosis before start of the therapy. At the same time, functional properties of peripheral blood ILC2 in patients with MGUS and MM were different from those in conditionally healthy individuals: the former had these cells developing cytotoxic activity against tumor cells. It is possible that such changes are associated with the differentiation of ILC2 into ILC1-like cells in MM patients [23], and the antitumor activity of such cells, on the one hand, may increase due to the polarization of the immune response towards T1 and the development of cytotoxic activity, and on the other hand, may be impaired in hematologic cancers, acute myeloblastic leukemia in particular [24].

CONCLUSIONS

Thus, MM patients exhibit changing ILC subpopulations composition, with ILC2 share growing and promoting polarization towards T2-type immune response. We have also shown that HLA-DR expression on the surface of the ILC2 cell membrane decreases, which lowers the ability to activate the immune response. Therefore, it is interesting to further study the mechanisms and features of polarization of the immune response, with one of such studies designed to comprehensively evaluate of production of T1/T2/T17 cytokines by various populations of regulatory cells in the cases of MM and other hematologic cancers. In addition, the search for potential targets for targeted therapy in MM patients remains relevant.

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