FEATURES OF THE IMMUNE RESPONSE TO TUMOR ALLOANTIGENS IN THE CONTEXT OF DECREASED CLONAL DIVERSITY OF T CELLS

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A T cell receptor (TCR), an αβ heterodimer, recognizes peptide antigens presented by self molecules of the major histocompatibility complex (MHC). A significant number of T cell clonotypes are alloreactive: they can interact with various allelic variants of MHC and the associated peptides. Currently, it is unclear whether the effectiveness of the allogeneic immune response depends on the diversity of the TCR repertoire. Seeking to experimentally narrow the diversity of T cell clonotypes, we used mice with transgenic expression of the β-chain TCR (TCRβ) in this work. We analyzed how the TCRß-transgenic mice on the CBA/Lac (H-2^k) background respond to EL-4 (H-$2K^b$) lymphoma cells *in vivo* with the aim to assess the effect of a narrower repertoire on the allogeneic immune response. The study has shown that transgenic mice develop a weak immune response to transplant antigens, and the formed pool of cytotoxic T cells is 1.5–1.7-fold smaller than that in wild-type animals. Consequently, the mice failed to reject the allogeneic tumor, leading to 100% mortality rate. The results of this work are consistent with the data from our earlier studies that employed another TCRß-transgenic model. They confirm that the decreased diversity of the TCR repertoire impairs the response to alloantigens, allowing the tumor to evade the immune response and progress in the allogeneic recipient.

Keywords: T-cell, T-cell receptor, allogeneic response, decreased clonal diversity

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ОСОБЕННОСТИ ИММУННОГО ОТВЕТА НА ОПУХОЛЕВЫЕ АЛЛОАНТИГЕНЫ В УСЛОВИЯХ СОКРАЩЕННОГО КЛОНАЛЬНОГО РАЗНООБРАЗИЯ Т-КЛЕТОК

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Т-клеточный рецептор (ТКР), представляющий собой αβ-гетеродимер, предназначен для распознавания пептидных антигенов в комплексе с собственными молекулами главного комплекса гистосовместимости (МНС). При этом значительная доля клонотипов Т-клеток обладает аллореактивностью, т. е. способностью взаимодействовать с различными аллельными вариантами МНС и ассоциированными с ними пептидами. В настоящее время нет четкой определенности, зависит ли эффективность аллогенного иммунного ответа от широты репертуара ТКР. В данной работе использовали мышей с трансгенной экспрессией β-цепи ТКР (ТКРβ), что позволило экспериментально сузить разнообразие клонотипов Т-клеток. Цель работы — проанализировать развитие ответа ТКРβ-трансгенных мышей на генетической основе CBA/Lac (H-2^k) на клетки лимфомы EL-4 (H-$2K^b$) *in vivo* для оценки влияния сужения репертуара на аллогенный иммунный ответ. Показано, что у трансгенных мышей развивается слабый иммунный ответ на трансплантационные антигены с формированием пула цитотоксических Т-клеток, в 1,5–1,7 раза сокращенного по сравнению с животными дикого типа. Вследствие этого отторжение аллогенной опухоли становится невозможным, и наступает гибель 100% животных. Полученные данные согласуются с результатами наших ранних исследований с использованием другой ТКРβ-трансгенной модели и подтверждают, что снижение разнообразия репертуара ТКР ухудшает эффективность ответа на аллоантигены и создает условия для избегания опухолью иммунного ответа и ее прогрессирования в аллогенном реципиенте.

Ключевые слова: Т-клетка, Т-клеточный рецептор, аллогенный ответ, сокращение клонального разнообразия

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T cells, the component of the adaptive immune system, can recognize antigens via the highly specialized T-cell receptor (TCR), which is an αß heterodimer in the dominant type of T-cells with the unique structure in each individual clonotype. The peripheral TCR repertoire matures and undergoes selection within the thymus; it is capable of effective interaction with the molecules of the major histocompatibility complex (MHC) that present a foreign peptide or a peptide of an endogenous mutant protein [1]. At that, a significant portion, if not all, clones of peripheral T-cells are alloreactive [2]; that is, they can react to allogeneic MHC molecules and the associated peptides [3–5]. Up to 10% of T-cells of the recipient's T-cell repertoire can participate in the response to an individual allogeneic transplant [6].

Alloreactive T-cells are the key mediators of transplant immunity that mediate acute allograft rejection [7]. Current knowledge is inconsistent regarding whether the diversity of the TCR repertoire determines the intensity of the allogeneic response; the available data are conflicting [8]. Several studies have shown an association between baseline high diversity of the recipient's TCR repertoire and an increased risk of acute rejection of allogeneic transplants [9, 10]. At the same time, it has been established that only a narrow oligoclonal repertoire is involved in graft rejection [11–13].

Experimental models involving transplantation of a tumor different in one transplant antigen [14, 15] enable *in vivo* exploration of the dynamics and features of development of allogeneic immune response. Direct recognition of allogeneic MHC class I molecules induces an intense cytotoxic $CD8^+$ T-cell response, and the allogeneic tumor is rapidly rejected, with immunological memory formed in the process [14–16]. In this work, we sought to confirm our earlier findings about the dependence of the effectiveness of the allogeneic immune response on the diversity of the TCR repertoire [14]. For this purpose, we used mice with transgenic expression of the β-chain TCR (TCRß) of hybridoma 7, which was described earlier [17]. TCRß transgenesis allows reducing the diversity of T-lymphocyte receptors [14, 18]: under the allelic exclusion rule, the expression of transgenic TCRß blocks gene rearrangement and, consequently, the expression of endogenous β-chains in T-cells. As a result, the repertoire becomes mainly comprised of clonotypes with an invariant β-chain, and its diversity stems only from the endogenous α-chains in the receptor structure.

This study aimed to analyze the development of the immune response to tumor alloantigens in the TCRβ transgenic model *in vivo*, in which the T-cell clonal diversity is reduced.

METHODS

We used female mice of the inbred lines CBA/Lac ($H\text{-}2^k$) and C57BL/6 ($H\text{-}2^b$) and transgenic mice 7B (6–8 weeks old, 18–20 g) bred at N.N. Blokhin National Medical Research Center of Oncology. The process of breeding the 7B transgenic mice was described earlier [18]. Initially, the transgene was transferred to the genetic background of C57BL/6 mice. Since the lifetime of the generated mice was limited, which hindered their breeding, the transgene was transferred to the genetic background of the CBA/Lac line; it is currently a part of the collection of the Laboratory of Regulatory Mechanisms in Immunity, Institute of Carcinogenesis (N.N. Blokhin National Medical Research Center of Oncology). 7B transgenic mice express the β-chain TCR, specific to the mutant MHC class I molecule K^{bm3} and the MHC class II molecule $I\text{-}A^b$ [17]. The animals were kept at 20–24 °C and 40% relative humidity, with a 12-hour light cycle, and had unrestricted access to feed and water. Transgenic 7B mice and control animals (non-transgenic wild-type siblings) were injected intraperitoneally with EL-4 ($H\text{-}2K^b$) lymphoma cells at a dose of 1×10^6 cells per mouse in 500 µl of phosphate-buffered saline (PBS). After injection, we monitored the life span of mice with a follow-up period of more than 30 days. The Kaplan-Meier survival curves were plotted using SRplot [19]. Some of the animals were removed from the experiment by cervical dislocation on the 12th day after EL-4 cell transplantation, with subsequent extraction of peritoneal cells. The obtained lavage cell samples were analyzed by flow cytometry.

We used fluorescently labeled antibodies (BioLegend, USA; BD Bioscience, USA; BD Horizon, USA): CD3 — APC-Cy7, CD8 — Percp-Cy5.5, CD44 — Pacific blue, CD62L — APC, Vb8.3 — PE, Kb — FITC. Cell samples ($0.5 – 1 \times 10^6$) were incubated with Fc block antibodies (clone 2.4G2, BD Pharmingen, USA) for 10 minutes at 4 °C to prevent nonspecific binding of antibodies, then stained with labeled antibodies for 40 minutes at 4 °C. For the analysis, we used a BD FACS Canto II flow cytometer (BD Bioscience) and the FACSDiva 6.0 software (BD Bioscience). Leukocytes were gated using forward scatter (FSC-A) and side scatter (SSC-A) parameters, and single cells were identified by plotting forward scatter height (FSC-H) against forward scatter area (FSC-A). The LIVE/DEAD fixable yellow dead cell stain kit (Invitrogen, USA) was used to stain dead cells; dead cells were excluded based on this staining and scatter parameters. The expression of surface markers was evaluated in a population of live single leukocytes. The relative number of T-lymphocytes expressing the transgenic TCR β-chain was assessed by staining with anti-Vb8.3 antibodies (the Vß family, to which the 7B transgenic β-chain belongs). The relative number of EL-4 tumor cells in the peritoneal cavity of experimental animals was determined by the expression of the MHC class I molecule $H\text{-}2K^b$ (Kb). The populations of T-lymphocytes were analyzed after exclusion of Kb-positive cells. The data was processed in the FlowJo 7.6 software (TreeStar Inc., USA). Figure 1 presents the cytofluorimetric analysis strategy.

The data are presented as the mean ± standard error of the mean. For statistical analysis, we used the Student's unpaired *t*-test, ANOVA, and the post-hoc Tukey test. The data samples were pre-checked for normality of the distribution using the Kolmogorov–Smirnov test, which confirms the validity of the selection of these statistical methods. For statistical analysis, we used the SRplot online service [19]. The differences were considered significant at $p \leq 0.05$.

RESULTS

As noted above, the transgenesis of the TCR β-chain significantly reduces the diversity of the peripheral TCR repertoire. Seeking to investigate the features of functioning of the T-cell immune system when the diversity of clonotypes is reduced, we studied the immune response of 7B transgenic mice ($H\text{-}2^k$) to allogeneic EL-4 lymphoma cells ($H\text{-}2K^b$) *in vivo*. T-lymphocytes at the transplantation site (in the peritoneal cavity) were analyzed on the 12^{th} day after EL-4 injection. Normally, by this day, the response of cytotoxic T-cells to EL-4 lymphoma alloantigens peaks [14, 16].

Immunized 7B mice (TG+EL-4) had the absolute number of cells in the peritoneal cavity increased by two orders of magnitude compared with intact (non-immunized) transgenic mice (TG) and 20-fold compared with immunized wild-type animals (WT+EL-4) (Fig. 2A). The lavage from the immunized 7B animals contained over 90% EL-4 (Kb^+) cells, whereas in control mice (WT+EL-4), the allogeneic tumor was almost completely eliminated by this time, and the proportion of Kb^+ cells was only 5% (Fig. 2B).

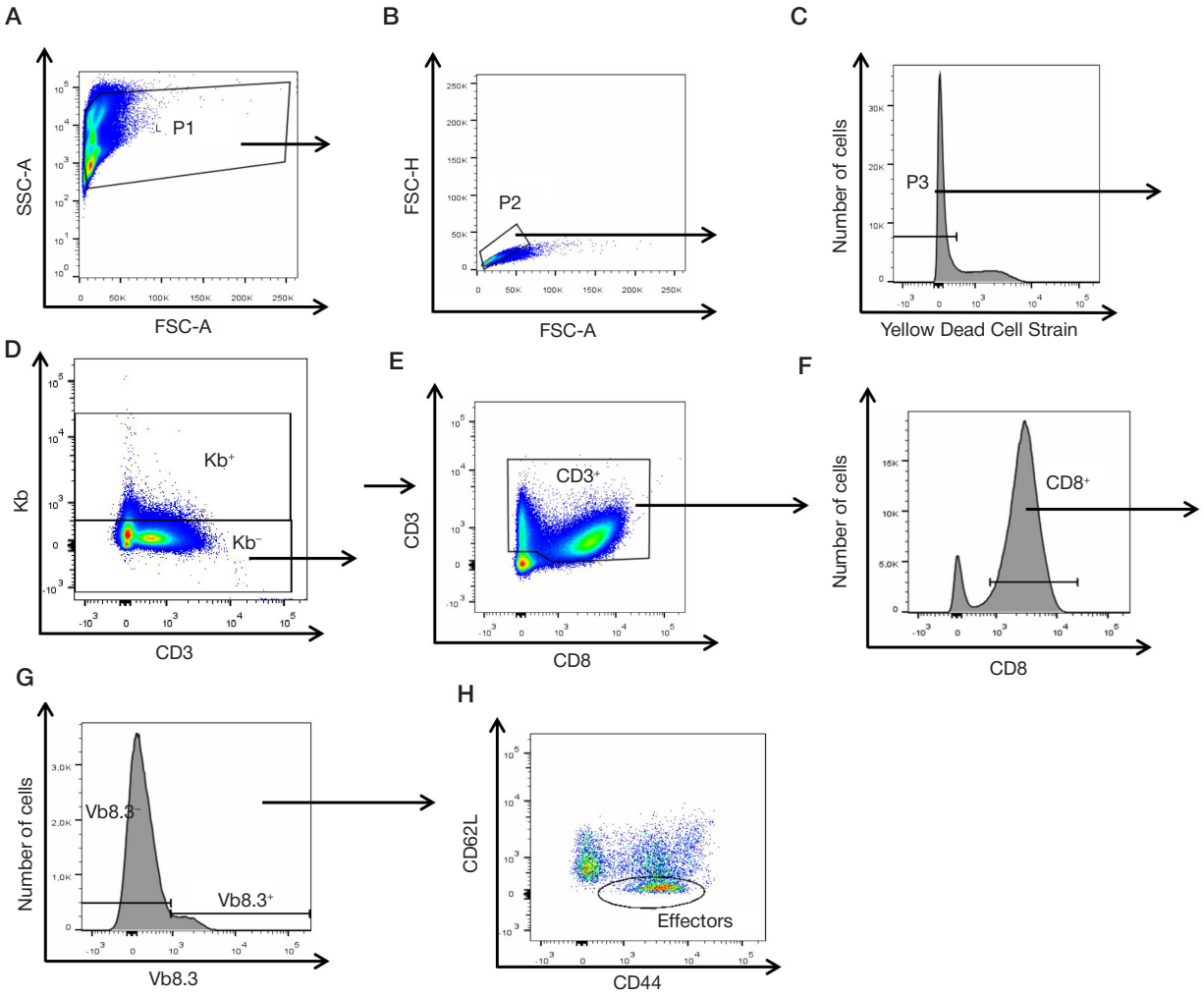

Fig. 1. Analysis of cells in the peritoneal cavity by flow cytometry (strategy). The analysis involved sequential gating of the following populations: leukocytes, gated by forward (FSC-A) and side (SSC-A) light scattering (P1) (**A**); single cells, gated by FSC-H vs. FSC-A (P2) (**B**); living cells negative as per yellow dead cell staining (P3) (**C**); EL-4 cells and recipient leukocytes, gated by co-expression of Kb and CD3 markers: Kb^+CD3^+ EL-4 cells (Kb^+), Kb-$CD3^+$ recipient cells (Kb^-) (**D**). **E**. In a population of Kb^-CD3^+ cells (Kb^-), T-cells ($CD3^+$) were gated by co-expression of CD3 and CD8 ($CD3^+CD8^+$ cells). **F**. Cytotoxic $CD8^+$ T-cells ($CD8^+$) were gated from the $CD3^+$- cell population. **G**. In the $CD8^+$ T-cell population, cells expressing endogenous β-chains of the T-cell receptor (TCRβ) ($Vb8.3^-$) and cells with the transgenic TCRβ ($Vb8.3^+$) were gated. **H**. For the $Vb8.3^-$ and $Vb8^+$ populations of $CD8^+$ T-cells, co-expression of CD44 and CD62L markers was analyzed, and the proportion (%) of effectors ($CD62L^-CD44^+$) was determined

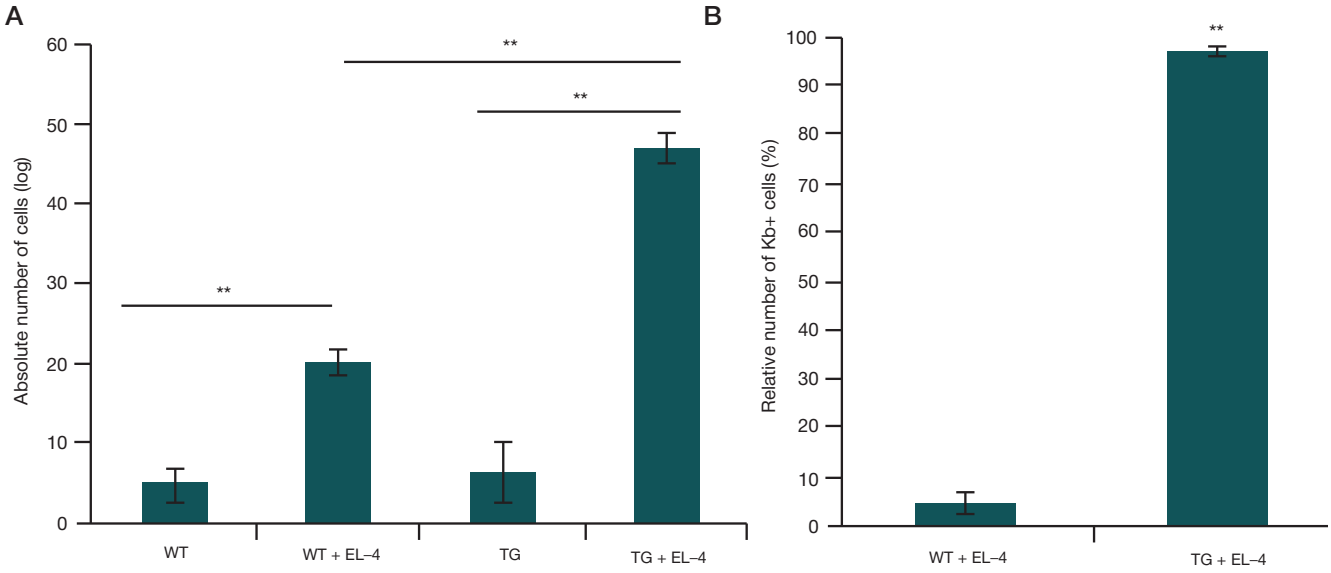

Fig. 2. Features of the development of EL-4 allogeneic lymphoma in 7B transgenic mice. Allogeneic lymphoma EL-4 ($H\text{-}2K^b$) cells were injected intraperitoneally to 7B ($H\text{-}2^k$) transgenic mice (TG+EL-4). Non-transgenic siblings (WT+EL-4) were used as controls. On day 12 after EL-4 injection, perinoteal cells were analyzed by flow cytometry. **A**. The absolute number (log) of cells. ** — $p \leq 0.01$ (ANOVA, post-hoc Tukey test). **B**. The relative number (%) of EL-4 (Kb^+) tumor cells. ** — $p \leq 0.01$ (Student's unpaired *t*-test). Data from two independent experiments ($n = 4–6$) are presented

7B mice were unable to reject allogeneic EL-4 lymphoma; as shown in Figure 3, all of them died after an average of 19 days. It should be noted that these animals endured longer than C57BL/6 mice, as for the latter, EL-4 is syngeneic and typically kills them within 10–12 days (Fig. 3). This finding indicates that in 7B transgenic mice, the response to allogeneic EL-4 lymphoma includes elimination and equilibrium phases — albeit insufficiently effective — before the tumor adapts to evade it.

The active immune response to EL-4 cells in wild-type mice (WT+EL-4) was characterized by an accumulation of T-cells, the number of which increased approximately fourfold (Fig. 4A, B), and a fivefold growth of the proportion of cytotoxic CD8⁺ cells compared with the intact control (WT) (Fig. 4C, D). Such developments were not registered in immunized transgenic mice (TG+EL-4): compared with the non-immunized control animals (TG), the relative number of T-lymphocytes (Fig. 4A, B) and CD8⁺ T-cells (Figure 4C, D) did not increase in them. However, the ratio of CD8⁺ T-cells expressing the transgenic β-chain TCR (Vb8.3⁺) or endogenous β-chains TCR (Vb8.3⁻) in the peritoneal cavity of immunized 7B mice (TG+EL-4) was approximately 1:1 compared with 2:1 in the control group (TG) (Fig. 4D, E), which indicates the involvement of both subpopulations of cytotoxic T-cells in response to EL-4 cells.

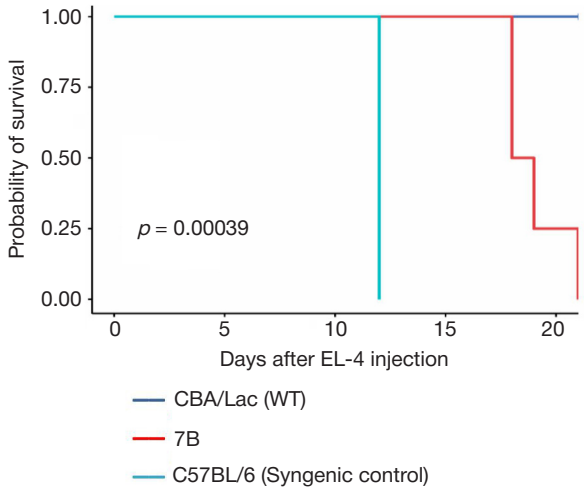

Fig. 3. Survival curves of 7B transgenic mice after EL-4 lymphoma transplantation. Parental CBA/Lac (WT) mice and C57BL/6 mice, for which EL-4 is a syngeneic tumor, were used as controls. The data from one representative experiment (n = 4) are presented

Accordingly, immunized 7B mice showed a 1.8-fold increase in the proportion of effector (CD44⁺CD62L⁻) CD8⁺ T-cells with transgenic TCRβ (Fig. 5A, B) and a 1.5-fold increase in effector CD8⁺ T-cells with endogenous TCRβ (Figure 5C, D), compared

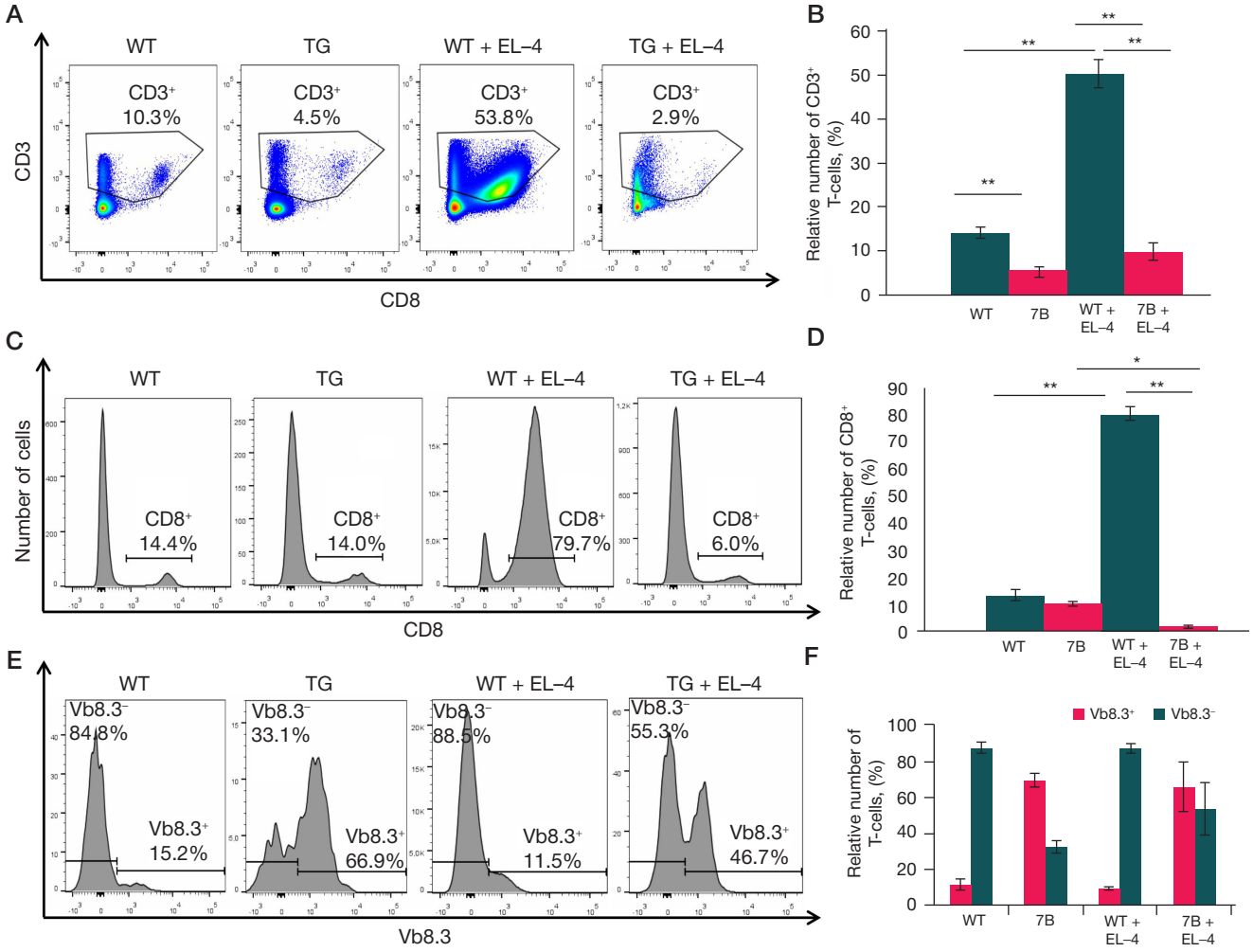

Fig. 4. Analysis of the immune response of 7B mice to an allogeneic tumor *in vivo*. Transgenic 7B mice (TG+EL-4) and non-transgenic siblings (WT+EL-4) were injected intraperitoneally with EL-4 allogeneic lymphoma cells. On day 12 after EL-4 injection, peritoneal cells were analyzed by flow cytometry. Intact (non-immunized) animals of the CBA/Lac (WT) parent line and the 7B (TG) transgenic line were used as controls. **A**, **B**. The relative number (%) of T-cells (CD3⁺). **C**, **D**. The relative number (%) of cytotoxic CD8⁺ T-cells. **E**, **F**. The relative number (%) of CD8⁺ T-cells with the transgenic β-chain of the T-cell receptor (TCRβ) (Vb8.3⁺) and CD8⁺ T-cells with endogenously rearranged TCRβ (Vb8.3⁻). **A**, **C**, **E**. Data from one representative staining are presented. **B**, **D**, **F**. Data from the two experiments are presented as the mean ± standard error of the mean (n = 4–6). * — $p \le 0.05$; ** — $p \le 0.01$, ANOVA, post-hoc Tukey test

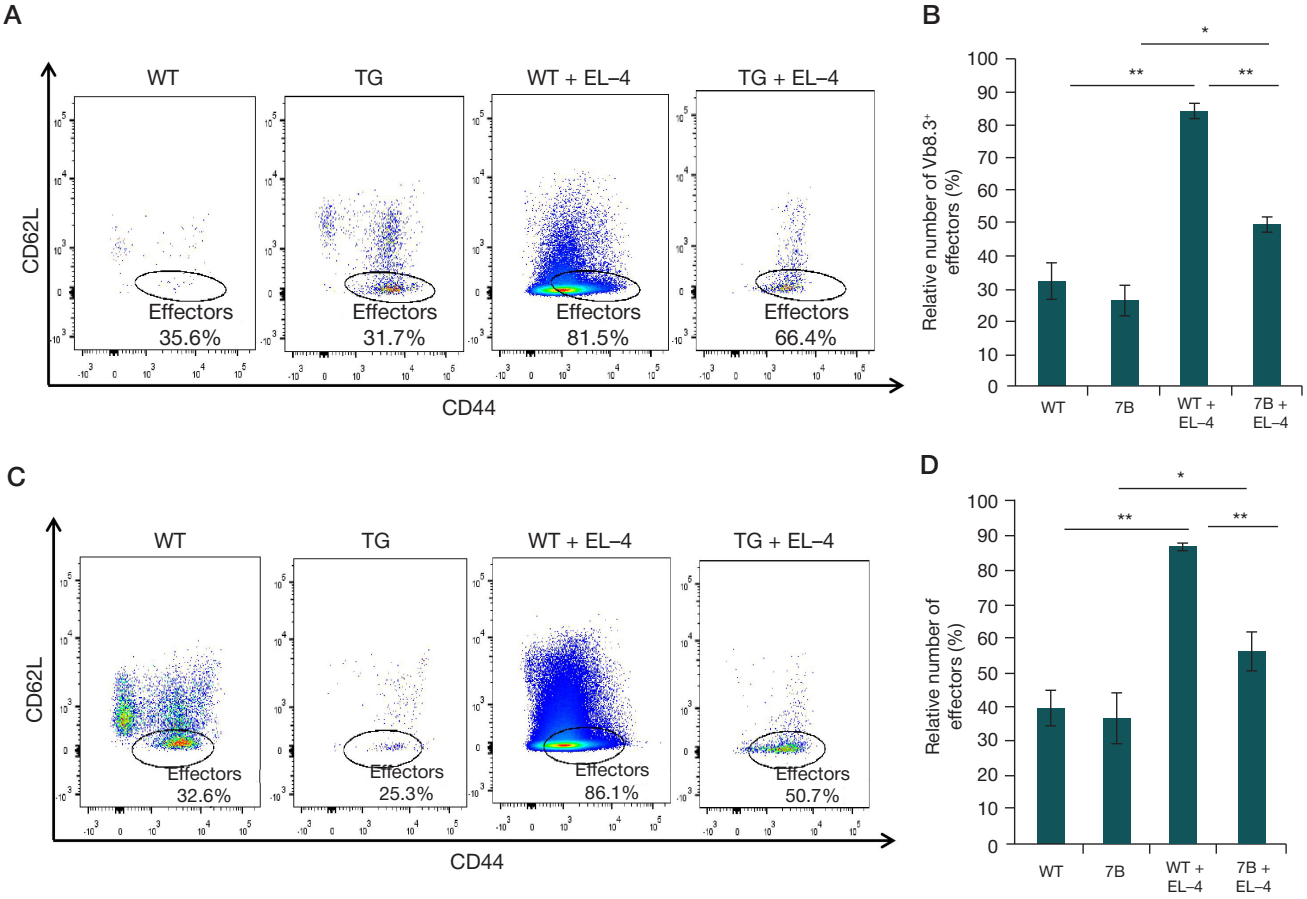

Fig. 5. Analysis of the pool of cytotoxic effector T-cells in 7B transgenic mice in response to EL-4 allogeneic lymphoma *in vivo*. Analysis of effector $CD44^+CD62L^-$ $CD8^+$ T-cells in the peritoneal cavity of 7B transgenic mice (TG+EL-4) and non-transgenic siblings (WT+EL-4) on day 12 after EL-4 injection. Intact (non-immunized) animals of the CBA/Lac (WT) parent line and the 7B (TG) transgenic line were used as controls. **A**, **B**. The relative number (%) of effector T-cells with transgenic TCRß ($Vb8.3^+$). **C**, **D**. The relative number (%) of effector T-cells with endogenously rearranged TCRß ($Vb8.3^-$). **A**, **C**. Data from one representative staining are presented. **B**, **D**. Data from the two experiments are presented as the mean ± standard error of the mean (n = 4–6). * — $p \le 0.05$; ** — $p \le 0.01$, ANOVA, post-hoc Tukey test

with the corresponding $CD44^+CD62L^-$ T-cell subpopulations in intact transgenic mice (TG). Meanwhile, the relative number of $Vb8.3^+$ and $Vb8.3^-$ $CD8^+$ effectors in the peritoneal cavity of immunized transgenic mice (TG+EL-4) was 1.5–1.7 times lower than in immunized wild-type animals (WT+EL-4) (50–56% vs. 84–86%) (Fig. 5).

DISCUSSION

The results of this study indicate the development of a weak immune response to alloantigens in 7B transgenic mice *in vivo* with the formation of a small pool of effector cytotoxic T-cells, which is consistent with the data of our early work that used a different TCRβ-transgenic model [14].

Several studies have shown that TCRß-transgenic animals retain the ability to respond to various antigens, including allogeneic MHC molecules [20, 21]. These findings point to the high plasticity of the TCR repertoire, which allows compensating for the significant reduction in the diversity of clonotypes caused by the expression of the transgenic β-chain [20, 21]. However, the intensity of the immune response in TCRß-transgenic mice is lower than in wild-type animals [14, 20, 21] because of the low frequency of responding T-cell clones [20, 22]; consequently, these mice show a slower development of T-cell responses *in vivo* [21]. An important factor in this context is that the cytotoxic $CD8^+$ immune response that TCRß-transgenic mice develop to the allogeneic MHC class I molecule ($H\text{-}2K^b$) is insufficient to reject the allogeneic tumor (Figure 4, Figure 5) [14]. Thus, the response even to a strong transplant antigen becomes ineffective due to the reduction of the diversity of the TCR repertoire.

In this regard, recognition of allogeneic tumor antigens follows the same patterns as recognition of tumor antigens in combination with self MHC molecules. The effectiveness of the antitumor response and, consequently, elimination of the transformed cells is largely determined by the mutation load of the tumor — its immunogenicity [23, 24] — and the clonal diversity of T-cells capable of recognizing tumor neoantigens or tumor-associated antigens [24, 25]. It has been shown that a high diversity of T-cell receptors (TCRs) circulating in peripheral blood is a favorable prognostic factor in several cancers, such as melanoma [26], non-small cell lung cancer [27, 28], and breast cancer [29]. In contrast, a low TCR diversity of tumor-infiltrating T-cells is associated with a poor prognosis in stomach cancer and some other malignancies [30–32].

The natural aging of the immune system, especially thymus involution and clonal expansion of memory cells in the periphery, causes a reduction in the diversity of the repertoire of T-lymphocytes [33-35], which leads to a greater predisposition of the elderly to infections and cancer [33, 36]. In addition, experimental studies involving mice have shown that at 12 months of age, the animals exhibit decreased responses to alloantigens, which are partly attributable to an age-associated narrowing of the T-cell clonotype repertoire [34, 37].

The results of this study confirm that the effectiveness of the immune response to tumor alloantigens directly depends on the breadth of the repertoire of mature T lymphocytes, as previously established [14].

CONCLUSIONS

This study shows that 7B transgenic mice develop an *in vivo* immune response that is not effective enough to eliminate allogeneic tumor cells. Due to the expression of the transgenic β-chain TCR, the number and frequency of cytotoxic T-cell clonotypes capable of recognizing allogeneic MHC molecules decrease. However, the neoplastic process in such animals progresses through all stages of immunoediting, from ineffective stages of elimination and equilibrium to the tumor escaping from immune surveillance. The results of this study are consistent with our earlier findings; they confirm that decreased diversity of the TCR repertoire is a factor preventing rejection of the allogeneic tumor, allowing it to progress. In this case, the weak immune response that develops in the allogeneic recipient contributes to the selection of the least immunogenic malignant clones, thereby driving tumor immunoediting.

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