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Attenuation of Acute Graft-versus-Host Disease in the Absence of the Transcription Factor RORγt

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Graft-versus-host disease (GVHD) remains the most significant complication after allogeneic stem cell transplantation. Previously, acute GVHD had been considered to be mediated predominantly by Th1-polarized T cells. Recently, investigators have identified a second proinflammatory lineage of T cells termed Th17 that is critically dependent on the transcription factor retinoic acid-related orphan receptor (ROR)γt. In this study, we have evaluated the role of Th17 cells in murine acute GVHD by infusing donor T cells lacking RORC and as a consequence the isoform RORγt. Recipients given donor CD4+ and CD8+ T cells lacking RORC had significantly attenuated acute GVHD and markedly decreased tissue pathology in the colon, liver, and lung. Using a clinically relevant haploidentical murine transplantation model, we showed that RORC−/− CD4+ T cells alone diminished the severity and lethality of acute GVHD. This was not found when CD4+ T cells from RORC−/− mice were given to completely mismatched BALB/c mice, and it was correlated with absolute differences in the generation of TNF in the colon after transplant. Thus, CD4+ T cell expression of RORC is important in the pathogenesis of acute GVHD. The Journal of Immunology, 2012, 189: 1765–1772.

Allogeneic stem cell transplantation (allo-SCT) is a common treatment for patients with high-risk leukemia, recurrent low-grade lymphomas, aplastic anemia, and congenital bone marrow failure syndromes (1–3). The effectiveness of allo-SCT is limited by the development of acute graft-versus-host disease (aGVHD). aGVHD, a disease characterized by selective epithelial damage to target organs, is mediated by mature T cells present in the stem cell or bone marrow inoculums (4–7). Interactions of donor T cells with predominantly host APCs leads to activation and differentiation of donor T cells, ultimately resulting in inflammation in GVHD target organs, which includes primarily the skin, liver, and gastrointestinal (GI) tract (8).

Previous GVHD research has focused on cytokine production in T cell subsets. High levels of IFN-γ and IL-2 found in patients after allo-SCT led investigators to conclude that GVHD was mediated predominantly by proinflammatory Th1 cells (9, 10). However and conversely, inhibition of Th1 cytokines leads to disease exacerbation in GVHD (11, 12). Because both protective and detrimental effects are seen with Th1 cytokines, the exact role of these cytokines in GVHD remains elusive (13). More recent investigations of T cell subsets in GVHD have been directed toward a new subset of CD4+ T cells, Th17 cells. Th17 cell differentiation and expansion requires TGF-β, IL-6, IL-23, TNF, and IL-1β (14–16).

The development of Th17 cells is dependent on the transcription factors retinoid-related orphan receptor (ROR)γt, RORα, IFN regulatory factor -4, and STAT3 (17, 18). Th17 cells produce proinflammatory cytokines such as TNF, IL-21, and IL-22 (19–21) that enhance production of G-CSF, IL-6, and chemokines that recruit neutrophils such as CXCL1 and CXCL8 (23).

Kappel et al. (24), using IL-17A knockout (+/−) CD4+ T cells, demonstrated that IL-17 contributes to aGVHD. In contrast, Yi et al. (25) has shown that IL-17A−/− T cells exacerbated aGVHD due to augmented release of IFN-γ. Recent studies in our laboratory demonstrated that in vitro-differentiated Th17 cells generated substantial cutaneous and pulmonary pathology in murine models of aGVHD (26), but multiple pathways may have been involved, with IL-17A and TNF being dominant. To better understand the effects of Th17 cells that are differentiated or activated in vivo, we elected not to focus on a particular cytokine effector pathway such as IL-17A itself, which would limit conclusions that can be drawn regarding Th17 cells. Instead, we performed studies using RORC−/− donor T cells that are incapable of producing the array of cytokines generated by Th17 cells, including IL-17A, IL-17F, IL-21, IL-22, and TNF. In the absence of...
RORC conventional T cells attenuated GVHD in a haploidentical, minor, and complete mismatched model. The absence of RORC expression by CD4+ T cells alone was sufficient to attenuate GVHD in the haploidentical model, but it had little impact on GVHD in a complete mismatched model. Interestingly, we found increased generation of IL-17 from lesional tissue in BALB/c recipient mice even when transplanted with donor T cells lacking RORC. These data indicate that T cell generation of RORγt is important to the pathogenesis of aGVHD.

Materials and Methods

Mice

C57BL/6J (H2b) (termed B6), BALB/cJ (H2d), C.B10-H2b/LiMcD1 (termed BALB.b), B6.129S6-Tbx21 tm1Glm (termed T-bet−/−), B6 × DBA/2 (F1) [B6D2 F1:H2 bxd], and B10.BR-H2d H2-T18a/SjSnJJrep mice (termed BALB.b), B6.129S6-Tbx21 tm1Glm were purchased from The Jackson Laboratory (Bar Harbor, ME). B6 RORC−/− mice were purchased as described (27). Donor and recipient mice were age-matched males between 8 and 16 wk. All experiments were performed in accordance with protocols approved by the University of North Carolina Institutional Animal and Care Use Committee.

Transplantation models

Total T cells or CD4+ T cells were isolated using Cedarlane T cell recovery kit (Cedarlane Laboratories, Burlington, ON), respectively, followed by Ab depletion using PE-conjugated anti-mouse B220 and anti-mouse CD25 Abs (eBioscience, San Diego, CA) and magnetic bead selection using anti-PE beads (Miltenyi Biotec, Cambridge, MA). Isolated CD4+ T cell were further purified using anti-mouse CD8 PE Ab. T cell-depleted bone marrow (TCD BM) and conventional T cells were prepared using previously described methods (28). Histopathology specimens were generated as described (29) and analyzed by one of us (A.P.M.) blinded to the genotype of donor used. Scoring of tissues was performed per our previous method (30).

Serum and organ cytokine analysis

Transplant recipient animals were anesthetized and perfused with PBS. Whole organs were removed and homogenized. Cytokine levels were measured using ELISA kits against IFN-γ, IL-17A, and TNF (BioLegend, San Diego, CA).

Intracellular cytokine staining

Single-cell suspensions of livers were digested using collagenase A and DNase I. Liver cells were stimulated with PMA, ionomycin, and brefeldin A for 4 h. Cells were harvested and stained for anti-mouse TNF (eBioScience, San Diego, CA) and anti-mouse B220 and anti-mouse CD25 Abs (eBioscience, San Diego, CA), respectively, followed by Ab depletion using PE-conjugated anti-mouse B220 and anti-mouse CD25 Abs (eBioscience, San Diego, CA). Lethally irradiated BALB/c mice given CD25-depleted donor Tconv from either WT or RORC−/− donors with WT TCD BM had improved median survival (Fig. 1C) with a diminished GVHD score (Fig. 1D) when receiving RORC−/− Tconv compared with WT Tconv. Similarly, the median survival was improved when BALB. B mice were administered RORC−/− Tconv compared with WT Tconv (Supplemental Fig. 1). However, in BALB.B recipients, there was only a transient improvement in GVHD score from days 10 to 17 after transplant. Thus, in three different GVHD models using CD25-depleted Tconv, the absence of RORC in donor T cells improved survival.

Decrease tissue pathology in GVHD target organs using RORC−/− donor T cells

Clinically, multiple organs can be affected in aGVHD, including the skin, liver, GI tract, and the lung. To determine whether RORC−/− Tconv affected aGVHD at a specific site, we evaluated the tissue pathophysiology in the liver, GI tract, lung, and spleen of RORC−/− Tconv recipients compared with WT Tconv recipients. Fifteen days after transplantation the organs of recipient animals were harvested and pathology analyses conducted. Recipients of RORC−/− Tconv displayed significantly less pathology in the liver, colon, lung, and spleen of RORC−/− Tconv recipients compared with WT Tconv recipients (p < 0.05, Fig. 2). Decreased pathology in recipient mice transplanted with RORC−/− donor Tconv was specific to GVHD target organs, as minimal GVHD pathology was detected in the kidney of WT and RORC−/− Tconv recipients. The aggressive nature of GI tract GVHD precluded the development of significant cutaneous GVHD in this model, and therefore cutaneous tissue was not evaluated. These data demonstrate that the function of RORC in the pathophysiology of aGVHD is not limited to a specific organ site.
RORC samples from IL-22. Cytokine analyses were performed on serum and organ to the pathogenesis of aGVHD such as TNF, IL-17F, IL-21, and/or Th17 cells generate a number of cytokines that may be important.

In vivo cytokine production using RORC<sup>−/−</sup> Tconv

Th17 cells generate a number of cytokines that may be important to the pathogenesis of aGVHD such as TNF, IL-17F, IL-21, and/or IL-22. Cytokine analyses were performed on serum and organ samples from RORC<sup>−/−</sup> Tconv versus WT Tconv in B6D2 F1 recipients on day 14 after transplantation. Interestingly, the administration of donor T cells unable to express RORC was associated with a modest increase in the production of IFN-γ in the serum of recipient mice compared with those receiving WT Tconv (Fig. 3A). A substantial decrease in IL-17 and TNF was seen in the serum of recipient RORC<sup>−/−</sup> Tconv compared with WT Tconv recipients (Fig. 3A). The decrease in TNF production in the serum was associated with statistically significant decreased production of TNF in the colon, but no differences were seen in cytokine production in other organs (Fig. 3B).

To determine whether the lack of differences in proinflammatory cytokines outside of the difference in the generation of TNF in the colon was due to the time point we evaluated, we analyzed mRNA expression of IFN-γ and IL-17A from lesional tissue on days 10 and 18 after transplantation. No difference was found in the expression of these cytokines in the colon, liver, or spleen of recipients of WT compared with RORC<sup>−/−</sup> T cells plus TCD B6 bone marrow (data not shown). Thus, the absence of RORC in donor T cells led to a marked decrease in the generation systemically of the proinflammatory cytokines TNF and IL-17A, and of TNF specifically in the colon.

RORC<sup>−/−</sup> CD4<sup>+</sup> T cells mediate GVHD in a haploidentical transplantation

Previous investigators have found that the infusion of donor T cells lacking RORC did not affect the incidence or severity of aGVHD when administered to lethally irradiated BALB/c recipients (34). However, the T cell inoculum for these experiments was comprised exclusively of CD4<sup>+</sup> T cells. The difference found by our group in the outcome of BALB/c recipients receiving RORC<sup>−/−</sup> T cells occurred when infusing CD4<sup>+</sup> and CD8<sup>+</sup> T cells. To determine whether the different T cell inocula mediate the changes in outcome initially, we confirmed the data from Icozlan et al. (34). BALB/c mice receiving RORC<sup>−/−</sup> CD4<sup>+</sup> T cells did not have improved survival or GVHD scores compared with recipients given WT CD4<sup>+</sup> T cells (Fig. 4A). Next, we determined whether the absence of RORC by donor CD4<sup>+</sup> T cells would impact the outcome in the haploidentical B6 into B6D2 model. All B6D2 recipients of RORC<sup>−/−</sup> CD4<sup>+</sup> T cells survived until completion of the experiment, with minimal evidence of clinical GVHD, whereas recipients of WT CD4<sup>+</sup> T cells succumbed to disease by day 35 after transplantation (Fig. 4B). This indicated that the difference in the outcome of recipient mice given donor RORC<sup>−/−</sup> CD4<sup>+</sup> T cells was model dependent. These data demonstrate a requirement for RORC CD4<sup>+</sup> T cell expression for GVHD pathogenesis in the haploidentical transplant setting.

Cytokine production in RORC<sup>−/−</sup> CD4<sup>+</sup> T cell recipents

Differences in outcome using RORC<sup>−/−</sup> CD4<sup>+</sup> T cells in the haploidentical versus the complete mismatch model are likely due to increased genetic disparity and potentially mismatched GVHD owing to the ability of a smaller number of donor T cells to mediate GVHD, or to GVHD mediated through different proin-
flammary pathways. To elucidate the differences in outcome using RORC−/− CD4+ T cells in the B6 into BALB/c transplant model compared with the B6 into B6D2 transplant model, we evaluated cytokine production in the serum and organs from recipient animals. Lethally irradiated B6D2 recipients were transplanted with 3 × 10^6 RORC−/− or WT CD4+ T cells with 3 × 10^6 WT TCD BM cells whereas lethally irradiated BALB/c recipients were infused with 5 × 10^5 RORC−/− or WT CD4+ T cells supplemented with 5 × 10^6 WT TCD BM cells. Serum and tissue homogenates from the liver, GI tract, lung, and spleen were collected from recipients 14 d after transplantation. We found that B6D2 recipients of RORC−/− CD4+ T cells had increased TNF production in the serum with decreased IFN-γ production compared with B6D2 recipients of WT CD4+ T cell (Fig. 4C), but neither of these values reached statistical significance. B6D2 recipients of RORC−/− CD4+ T cells had a significant decrease in the production of TNF and IFN-γ in the colon compared with B6D2 recipients of WT CD4+ T cells (Fig. 4D). This was not found in BALB/c recipients given either RORC−/− or WT donor CD4+ T cells. Interestingly, IL-17 production in the liver of BALB/c recipients was 8-fold higher than IL-17 production in the liver and colon of B10.BR recipients did not differ in the absence of RORC−/−. Interestingly, similar to BALB/c recipients, increased expression of IL-17 was seen in recipient B10.BR mice given either RORC−/− or WT CD4+ T cells (Fig. 4D). These data suggest that the generation of IL-17A in the completely mismatched MHC transplant models is more dependent on production by cells other than donor T cells. Moreover, we found that the absence of RORC in donor T cells mediated protection against GVHD only in models in which there was a decrease in the production of TNF systemically and in the colon after the infusion of RORC−/− T cells.

**RORC and TNF production**

Our data indicate a role for RORC in the function of CD4+ T cells in the haploidentical transplant model. To determine whether there was a function for RORC in donor CD8+ T cells, we transplanted mice with either RORC−/− or WT CD4+ or CD8+ T cells. Three cohorts of lethally irradiated B6D2 F1 recipients were used for these experiments. One group received 2 × 10^6 RORC−/− CD4+ T cells with 2 × 10^6 WT CD8+ T cells supplemented with 3 × 10^6 TCD BM cells. A second group received 2 × 10^6 WT CD4+ T cells with RORC−/− CD8+ T cells supplemented with 3 × 10^6 WT TCD BM cells. A final group received only 3 × 10^6 TCD BM cells. Interestingly, >80% of mice that received RORC−/− CD4+ T cells with WT CD8+ T cells survived until day 50 after transplantation, whereas those receiving WT CD4+ T cells with RORC−/− CD8+ T cells died of GVHD by day 30 after transplantation (Fig. 5A). Intracellular cytokine analyses of TNF and IFN-γ production were conducted on T cells isolated from liver of WT CD4+ T cells (Fig. 5B). These data suggest that the production of TNF by CD4+ and not CD8+ T cells is critical to the pathogenesis of GVHD in this model.

**Tissue-specific role for T-bet in aGVHD**

To determine whether the inability to produce proinflammatory cytokines was sufficient to attenuate aGVHD, we investigated the transcription factor that controls the expression of the Th1 cytokine IFN-γ, Tbx21 (T-bet). Donor CD25+ Tconv from T-bet−/− or WT
mice supplemented with WT TCD BM were transplanted into lethally irradiated B6D2 F1 recipients. Interestingly, in this model, no difference was found in survival or GVHD score in mice re-ceiving WT compared with T-bet−/− Tconv (Fig. 6A). However, analysis 15 d after transplantation revealed statistically significant decreased pathology in the ileum of recipients of T-bet−/− compared with WT CD4+ T cells supplemented with 3 × 10^6 WT TCD BM (n = 7 for T-bet−/− CD4+ T cells, n = 7 for WT CD4+ T cells, n = 3 bone marrow only). Data indicate p < 0.05 for survival and p < 0.05 from day 17 until the completion of the experiment for the difference in GVHD score. Data are combined from two individual experiments. (C) Serum and (D) organs were harvested from lethally irradiated BALB/c, B6D2 F1, or B10.BR recipients transplanted with T-bet−/− or WT CD4+ T cells 14 d after transplantation. WT B10.BR recipients were harvested 10 d after transplantation. TNF, IFN-γ, and IL-17 production were determined by ELISA. Data were pooled from five T-bet−/− CD4+ T cell BALB/c recipients and four WT CD4+ T cell BALB/c recipients, six T-bet−/− CD4+ T cell B6D2 recipients and four WT CD4+ T cell B6D2 recipients, and four T-bet−/− CD4+ T cell B10.BR and three WT CD4+ T cell B10.BR recipients. Statistical analysis was determined by a Mann–Whitney U test. *p < 0.05.

**Graft-versus-leukemia response in the absence of RORC**

Next, we addressed whether the loss of RORC would impact the antitumor activity of SCT. Antitumor activity after transplantation was evaluated by adding 1 × 10^4 P815 cells to the donor bone marrow inoculum on day 0. One group of B6D2 F1 mice received RORC−/− Tconv in addition to WT TCD BM cells infused with P815 tumor cells. Because recipients of WT Tconv often succumb to GVHD before antitumor properties can be analyzed, syngeneic controls were given B6D2 Tconv supplemented with WT TCD BM infused with P815 tumor cells. Control mice received only WT TCD BM infused with P815 tumor cells. All mice receiving only WT TCD BM with P815 tumor cells died by day 20 due to tumor infiltration. Recipient mice receiving B6D2 Tconv died by day 20 due to tumor growth. Recipient mice receiving B6D2 Tconv died by day 20 due to tumor infiltration (Fig. 7). Interestingly, survival was extended to day 40 in recipient mice given RORC−/− Tconv and P815 cells, indicating that the graft-versus-leukemia (GvL) response remained somewhat intact in mice given T cells lacking RORC. To demonstrate that this difference was not mediated by donor bone marrow cells, we administered RORC−/− TCD BM or WT TCD BM cells plus P815 cells to lethally irradiated B6D2 F1 recipient mice. As expected, all recipient mice succumbed to tumor infiltration by day 30 (data not shown).
Discussion

Acute GVHD is mediated by donor T cells that recognize minor or major MHC disparities presented predominantly by host APCs. This process leads to activation, differentiation, and T cell effector responses that are critical for the pathophysiology of aGVHD. During the past decade multiple investigators have identified new T cell subsets characterized by the activity of canonical transcription factors and the generation of specific cytokines. The T cell subsets critical for the pathophysiology of aGVHD are currently unclear and are the focus of this manuscript. In this study, we find unexpectedly that the loss of the Th17 transcription factor, \( RORC \), in donor CD25-depleted T cells led to markedly diminished aGVHD. In three different models, recipient mice given \( RORC^{2/2} \) Tconv had significantly less GVHD and increased survival compared with recipients given WT Tconv. The absence of \( RORC \) was associated with diminished GVHD in all target organs evaluated and correlated with diminished systemic generation of proinflammatory cytokines. The difference in pathology of GVHD target organs was not associated with a difference in frequency of regulatory T cells in these organs after transplant (L.M. Fulton and J.S. Serody, unpublished observations). As was previously found, the absence of \( RORC \) on CD4+ T cells had no effect on GVHD outcome in a completely mismatched B6 into BALB/c model. Interestingly, in the B6 into B6D2 model, the absence of T-bet in donor T cells led to diminished pathology in the GI tract but no overall survival benefit. When challenged with P815 tumor cells, recipient mice receiving donor T cells lacking \( RORC \) survived longer than did mice receiving bone marrow alone, indicating the presence of an antitumor GvL response. However, in both instances recipient mice succumbed eventually to tumor growth, indicating that the GvL response is modestly compromised using T cells unable to generate \( RORC \), perhaps because of the diminished generation of TNF.

Previous work has clearly indicated a critical role for Th1/Tc1 T cells in the pathophysiology of aGVHD particularly involving the GI tract. Thus, it was somewhat unexpected that the absence of T-bet alone, although diminishing GVHD in the small bowel and to a lesser extent in the colon, was not associated with an improved overall survival. T-bet has been found to be critical for the generation of IFN-\( \gamma \) by CD4+ T cells and NK cells. However, the generation of IFN-\( \gamma \) by CD8+ T cells is not impaired in the absence of T-bet, which may be responsible for the similar survival (36). As we have found that \( RORC \) is required in the CD4+ T cell compartment, our data would be consistent with a role for IFN-\( \gamma \) generation by CD8+ T cells and TNF production by CD4+ T cells in the pathogenesis of aGVHD.

Quite recently, Yu et al. (37) evaluated the ability of T cells from mice deficient in \( RORC \) or \( Tbx21 \) to induce GVHD. They found diminished GVHD using T cells from B6 \( Tbx21^{2/2} \) donors, but no
target organs. Our data confirm and extend these findings as they
receptors important for the trafficking of donor T cells to GVHD
deleted only when TNF production was diminished by CD4 +
activity of donor T cells. In this study, we found that donor T cells
elimination of GVHD without compromising the antitumor GvL
activity of donor T cells. In this study, we found that donor T cells
lacking RORC still mediated an antitumor response against the
mastocytoma cell line, P815. Killing of P815 cells is dependent on
the generation of dual-positive IL-17A/IFN-γ T cells when WT
Tconv were infused compared with WT TCD BM. B6D2 recipient
mice were lethally irradiated (950 cGy) on day −1. Following irradiation on day 0 mice were injected i.v. with 4 × 106 WT or T-bet−/− Tconv supplemented with 3 × 106 WT TCD BM. Mice were monitored for survival and scored twice weekly for clinical GVHD (n = 14 for T-bet−/− recipients, n = 11 for WT recipients, n = 4 bone marrow only). All recipient mice receiving BM only cells survived until the completion of the experiment. (B) On day 15 after transplantation organs were harvested from WT and T-bet−/− recipients and evaluated for pathology as described above. Error bars indicate SEM. Statistical significance was determined using a Mann–Whitney U test. Data are combined from two individual experiments. *p < 0.05, #p = 0.09.

We found a substantial difference in the generation of TNF and
IL-17A in the serum and TNF in the colon of recipient mice given
RORC−/− compared with WT T cells. Our previous data have indicated that TNF is critical for the systemic manifestations of GVHD mediated by Th17 cells. Interestingly, in this study we found that TNF production by CD4+ and/or CD8+ T cells was markedly reduced when that subset did not express RORC. However, this was compensated for by production of TNF from the WT T cells when both were given. However, GVHD was decreased only when TNF production was diminished by CD4+ T cells and not from CD8+ T cells, indicating cell-intrinsic differences in the function of TNF after SCT. We found an increase in the generation of dual-positive IL-17A/IFN-γ T cells when WT Tconv were infused compared with RORC−/− Tconv 12 d after transplantation (Supplemental Fig. 2). The generation of these cells, which may eventually become Th1 cells (M.J. Carlson and J.S. Serody, unpublished observations), may be one mechanism for the decreased incidence and severity of aGVHD after the infusion of T cells unable to generate RORC.

For allogeneic transplantation to be successful requires the elimination of GVHD without compromising the antitumor GvL activity of donor T cells. In this study, we found that donor T cells lacking RORC still mediated an antitumor response against the mastocytoma cell line, P815. Killing of P815 cells is dependent on the generation of IFN-γ and TNF (38). This suggests that the decreased generation of TNF in the absence of RORC is not

![FIGURE 6.](https://example.com/figure6.png) Tconv decrease pathology in the GI tract but do not attenuate GVHD. (A) B6D2 F1 recipient mice were lethally irradiated (950 cGy) on day −1. Following irradiation on day 0 mice were injected i.v. with 4 × 106 WT or T-bet−/− Tconv supplemented with 3 × 106 WT TCD BM. Mice were monitored for survival and scored twice weekly for clinical GVHD (n = 14 for T-bet−/− recipients, n = 11 for WT recipients, n = 4 bone marrow only). All recipients mice receiving BM only cells survived until the completion of the experiment. (B) On day 15 after transplantation organs were harvested from WT and T-bet−/− recipients and evaluated for pathology as described above. Error bars indicate SEM. Statistical significance was determined using a Mann–Whitney U test. Data are combined from two individual experiments. *p < 0.05, #p = 0.09.

![FIGURE 7.](https://example.com/figure7.png) Improved antitumor responses in the absence of RORC. Lethally irradiated B6D2 F1 mice were injected with 3 × 106 TCD BM with or without 4 × 106 WT or RORC−/− Tconv. Additionally, all recipient mice received 1 × 104 P815 cells with the BM inoculum. Survival was determined by the Kaplan–Meier method. An improvement in overall survival was found in B6D2 F1 mice given RORC−/− Tconv compared with B6D2 T cells or BM plus P815 cells (p < 0.05) (n = 7 recipients receiving RORC−/− T cells, n = 5 recipients receiving B6D2 T cells, n = 4 recipients receiving bone marrow). Data are combined from two individual experiments.
sufficient to completely lose the antitumor activity of donor T cells.

In summary, we have shown that donor T cells lacking RORC do not mediate substantial aGVHD in three different transplant models. This finding is dependent on the absence of RORC in CD4+ T cells, correlated with reduced generation of TNF and IL-17A systemically and TNF in the colon, and was important for the diminished GVHD that occurred in clinically relevant transplant models.

Disclosures

The authors have no financial conflicts of interest.

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