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Sphingosine-1-Phosphate Receptor Agonism Impairs the Efficiency of the Local Immune Response by Altering Trafficking of Naive and Antigen-Activated CD4$^+$ T Cells

Jenny H. Xie,[1]* Naomi Nomura,* Sam L. Koprak,† Elizabeth J. Quackenbush,* Michael J. Forrest,* and Hugh Rosen[2†]

FTY720 (2-amino-[2-(4-octylphenyl) ethyl]-1,3-propanediol hydrochloride) is an immunosuppressive agent that inhibits allograft rejection. We recently demonstrated that FTY-phosphate, the active metabolite of FTY720, acts as a full agonist for sphingosine-1-phosphate (S1P) receptors. Furthermore, activation of S1P receptors with their natural ligand, S1P, as well as pharmacological ligands leads to lymphopenia, probably due to sequestration of lymphocytes in secondary lymphoid organs. In the present study we used a local Ag-challenged mouse model to examine the effects of FTY720 on T cell activation in the draining lymph node (DLN) and on the release of activated T cells to the peripheral blood compartment. We showed that the number of Ag-activated CD4$^+$ T cells in the DLN after injection of Ag and CFA into a footpad was dramatically reduced after FTY720 treatment. However, T cell proliferation, both in vitro and in vivo, was not impaired by FTY720. Our results suggest that the reduced efficiency of T cell responses in the DLN in response to a local Ag is probably due to a defective recirculation of naive T cells caused by FTY720 treatment. Furthermore, we found that the numbers of naive and Ag-activated CD4$^+$ T cells in the peripheral blood of Ag-challenged mice were equally reduced with FTY720 treatment, suggesting that both T cell subsets are sequestered in the DLNs. Thus, FTY720 induces immunosuppression through inhibition of both the recirculation of naive T cells and the release of Ag-activated T cells from the DLN to lymph and to the blood compartment. ***The Journal of Immunology,*** **2003, 170: 3662–3670.**

FTY720 is a potent immunomodulator that has been shown to prolong the survival of solid organ allografts, including skin (1–3), heart (4, 5), liver (6–10), and small bowel (7, 11) in animal models. FTY720 has unique modes of action and shows synergy with cyclosporin and sirolimus in these models (7, 12). A striking feature of FTY720 activity is the induction of a marked decrease in the number of circulating mononuclear cells, especially T cells, at doses that prolong allograft survival. Recently, we have identified a phosphate ester metabolite of FTY720 that acts as a full agonist for the sphingosine-1-phosphate (S1P)[3] receptors $S1P_1$ (edg1), $S1P_3$ (edg3), $S1P_4$ (edg6), and $S1P_5$ (edg8). Activation of S1P receptors by their natural ligand, S1P, as well as by pharmacological ligands results in lymphopenia, which is largely due to enhanced retention of lymphocytes in secondary lymphoid organs (13). Within 3 h of FTY720 administration, there is emptying of lymphoid sinuses and an absence of their egress into lymph.

Cell-mediated immune responses include initial T cell activation by APCs in the lymph nodes and subsequent trafficking of activated T cells to sites of inflammation. Numerous studies have demonstrated that FTY720 is efficacious in prolonging allograft rejection and preventing development of autoimmune diseases (14). However, few studies have been focused on dissecting the mechanisms for FTY720-mediated immunosuppression. It is known that for immune surveillance, naive T cells circulate from lymph node to lymph node until they encounter their Ag in the specialized lymph node microenvironment. With FTY720 treatment, T cell recirculation is inhibited to a large extent as T cells are sequestered in individual lymph nodes and Peyer's patches. Whether defective T cell circulation can affect T cell responses in the lymph nodes remains unclear. Pinschewer et al. (15) have reported that FTY720 has no measurable effect on the induction or expansion of cytotoxic cells in a systemic virus infection model. We reason that T cell circulation is more critical in a localized immune response because it ensures that those T cells that carry the right TCR have the chance to encounter their Ag in a particular region of the body. Therefore, the effect of FTY720 on T cell responses in the draining lymph node (DLN) needs to be further examined in a local Ag-challenged model.

Differential migratory properties have been directly demonstrated for naive, effector, and memory T cells (16, 17). Naive T cells are thought to be incapable of homing to inflammatory tissues due to the absence of appropriate adhesion molecules that are essential for transendothelial migration at peripheral sites. On the contrary, activated T cells express adhesion molecules, including functional selectin ligand and chemokine receptors as a result of Ag and cytokine stimulation and therefore, are capable of migrating to peripheral sites of Ag (16) (data not shown). Infiltrated lymphocytes at peripheral sites further proliferate and produce cytokines in response to specific Ag to amplify local inflammatory responses. Thus, preventing activated T cells from homing to the peripheral site of Ag can lead to immunosuppression in diseases that are T cell mediated and directed against peripherally located tissues, such as allotransplantation and organ-specific autoimmune

Departments of *Pharmacology and †Immunology and Rheumatology, Merck Research Laboratories, Rahway NJ 07065

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[1] Address correspondence and reprint requests to Dr. Jenny H. Xie, R80Y-125, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065. E-mail address: jenny_xie@merck.com

[2] Current address: The Scripps Research Institute, ICND-118, La Jolla, CA 92037.

[3] Abbreviations used in this paper: S1P, sphingosine-1-phosphate; BrdU, 5-bromodeoxyuridine; CMFDA, 5-chloromethylfluorescein diacetate; DLN, draining lymph node; GT, Green Tracker; PCC, pigeon cytochrome c_{88-104}.

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diseases. To date, few studies have focused on the roles of FTY720 in altering the trafficking of T effector/memory populations. Pinschewer and colleagues (15) have shown that the number of adoptively transferred Ag-specific $V\alpha2^+V\beta8^+$ cells after 8-day viral Ag stimulation is greatly reduced with FTY720. However, $V\alpha2^+V\beta8^+$ cells are a mixed population of naive and effector T cells in peripheral blood. Furthermore, the dose requirement for reducing the number of effector vs naive T cells in peripheral blood is not known.

In the studies presented here we have examined the effect of FTY720 on T cell-mediated responses, including T cell expansion in the DLN and subsequent release of activated T cells to the peripheral blood compartment. By adoptively transferring naive DO11.10 TCR transgenic $CD4^+$ cells to syngeneic recipients followed by footpad injection of Ag and adjuvant, we showed that FTY720 treatment led to reduced expansion of Ag-specific T cells in the DLN. We also demonstrated that FTY720 caused a significant reduction in the number of activated T cells in peripheral blood when T cell priming occurs under FTY720 treatment.

Materials and Methods

Mice

BALB/c mice were purchased from Taconic Farms (Germantown, NY). DO11.10 TCR transgenic mice (18) were purchased from The Jackson Laboratory (Bar Harbor, ME). DO11.10 mice express the DO.11.10 TCR, specific for the chicken OVA peptide $OVA_{323–339}$ in the context of the MHC class II molecule $I\text{-}A^d$. They have been backcrossed 15 generations onto the BALB/c background and are histocompatible with normal BALB/c mice. The AND TCR transgenic mice expressing an α/β TCR ($V\alpha11$, $V\beta3$), specific for pigeon cytochrome $c_{88–104}$ (PCC) (19), were purchased from The Jackson Laboratory, where they have been backcrossed to the B10.BR strain for five generations. Mice were further backcrossed to the B10.BR mice for seven generations at Merck Research Laboratories (Rahway, NJ).

In vitro MLR

Irradiated splenic cells (800 rad; 100 μl at 5×10^6/ml) from C57BL/6 mice were cultured with BALB/c splenic cells (100 μl at 5×10^6/ml) in RPMI 1640 medium (Cellgro; Mediatec, Washington, D.C.) supplemented with 2 mM L-glutamine, 10 mM HEPES, 1 mM sodium pyruvate, 0.1 mM nonessential amino acids, 50 μg/ml gentamicin, and 10% FCS. Cells were treated with various doses of FTY720 or FTY720-phosphate. Three days later, cells were pulsed with [^{3}H]thymidine (2 μCi/well), and the next day incorporation of [^{3}H]thymidine was measured with an LKB 1205 Betaplate liquid scintillation counter (Wallac, Gaithersburg, MD).

Generation of in vitro polarized Th1 cells

T cell differentiation was induced by culturing splenic cells from AND TCR mice (at 2×10^6/ml) with1 μM PCC peptide plus 2 ng/ml IL-2 and 10 ng/ml IL-12. Cultures were fed with fresh medium (supplemented with peptide and appropriate cytokines) on days 2 and 4. Cells were harvested on day 6 and labeled with 1 μM Green Tracker (GT; 5-chloromethylfluorescein diacetate (CMFDA); Molecular Probes, Eugene, OR) before adoptive transfer to irradiated (750 rad) B10.BR mice through tail vein injection (1.5×10^7/mouse). In some cases, naive splenic cells from AND TCR mice were adoptively transferred to irradiated B10.BR mice (5×10^7/mouse). After 24 h mice were treated with vehicle or FTY720 (1 mg/kg orally). Peripheral blood was collected 18 h later, and the percentage of CMFDA-positive $CD4^+$ T cells was determined by flow cytometry.

Adoptive transfer and Ag challenge

Splenocytes from DO11.10 mice were adoptively transferred into nonirradiated BALB/c mice by i.v. injection (3×10^7/mouse). On the following day the BALB/c recipients were treated with various doses of FTY720 orally or with 1 mg/kg rapamycin (Wyeth Laboratories, Philadelphia, PA) i.p. After 4 h mice were given footpad injections of 100 μg of OVA (Sigma-Aldrich, St. Louis, MO) or PBS emulsified in the same volume of CFA (Sigma-Aldrich) in a total volume of 50 μl. FTY720 (orally) and rapamycin (i.p.) were administered daily until 1 day before harvest. Draining popliteal nodes (Ag-challenged side), nondraining popliteal nodes (contralateral side), and peripheral blood were collected at various times after Ag challenge. Cell suspensions were prepared, counted with a hemocytometer, stained with Abs, and then analyzed by flow cytometry.

Flow cytometric analysis

Popliteal node cells were stained with allophycocyanin-labeled anti-CD4 mAb (BD PharMingen, San Diego, CA) and PE-labeled KJ126 mAb (Caltag, Burlingame, CA), which binds exclusively to the DO11.10 TCR. Twenty thousand events were collected for each sample on a FACSCalibur flow cytometer (BD Bioscience, Mountain View, CA) and analyzed using CellQuest (BD Bioscience). The number of DO11.10 T cells that were identified as $CD4^+KJ126^+$ cells was calculated by multiplying the total lymph node cells counted with a hemocytometer by the percentage of $CD4^+KJ126^+$ cells determined by flow cytometry.

Peripheral blood samples were diluted 1/5 with PBS, layered on the same volume of Lymphocyte Separation Medium (ICN Biomedical, Aurora, OH), and centrifuged at $400 \times g$ for 30 min. PBMC were resuspended in PBS, counted with a hemocytometer, and stained with allophycocyanin-labeled anti-CD4 mAb.

Measurement of cell cycle progression by CFSE in vivo

In some experiments DO11.10 splenocytes were labeled with 5 μM CFSE (Molecular Probes) before adoptive transfer to monitor cell cycle progression. FL-1 fluorescence was measured in $CD4^+KJ126^+$ T cells at various times after stimulation, and cells demonstrated a 2-fold decrease in FL-1 fluorescence with each successive round of cell division. Two hundred thousand events were collected for lymph node and PBMC samples using a FACSCalibur flow cytometer.

Measurement of in vivo T cell proliferation by 5-bromodeoxyuridine (BrdU) incorporation

BrdU (1 mg) was injected i.p. on day 2 after OVA CFA injection in the DO11.10 adoptive transfer model described above. The draining popliteal node was collected the next day and stained with anti-CD4-allophycocyanin, KJ126-PE, and anti-BrdU-FITC according to the manufacturer's instructions (BD PharMingen).

In vivo MLR

FTY720 (0.5 mg/kg/day) was administered orally to C57BL/6 mice. After 4 h mice were given footpad injections of 1.5×10^7 BALB/c splenocytes. The draining popliteal nodes were harvested 3 days after alloantigen challenge, and DLN cells were counted with a hemocytometer.

Results

Reduced expansion in number of Ag-specific T cells by FTY720 in DLN of Ag-challenged mice

In this study Ag-mediated T cell responses in the DLN were examined by adoptive transfer of DO11.10 splenocytes to syngeneic BALB/c mice, followed by footpad injection with OVA Ag emulsified in CFA. The donor DO11.10 T cells were detected by flow cytometry using the anticlonotypic mAb, KJ126. Clonal expansion of $CD4^+KJ126^+$ cells occurred after Ag stimulation. The percentage of $CD4^+KJ126^+$ cells in the DLN (popliteal node from the Ag-injected side) was typically between 8–10% by day 3 after Ag challenge compared with 0.5% from nontreated mice (data not shown). The absolute number of $CD4^+KJ126^+$ cells, calculated by the total lymph node cell count multiplied by the percentage of $CD4^+KJ126^+$ cells, was typically increased by 50- to 80-fold (66-fold shown in Fig. 1*A*) compared with nontreated mice. This T cell response required Ag, as adjuvant alone increased the number of $CD4^+KJ126^+$ T cells by only 2-fold (Fig. 1*A*).

To investigate the effect of FTY720 on T cell expansion in this Ag-induced model, mice were treated orally with 0.5 mg/kg FTY720 4 h before footpad injection of OVA CFA and then daily with the same dose until 1 day before harvest. We first examined the number of Ag-specific T cells 4 h post-FTY720 treatment without Ag challenge. As expected, they were depleted from the peripheral blood compartment but present in all secondary lymphoid organs, including the popliteal lymph node, which is the regional node for an Ag delivered through the footpad (data not shown).

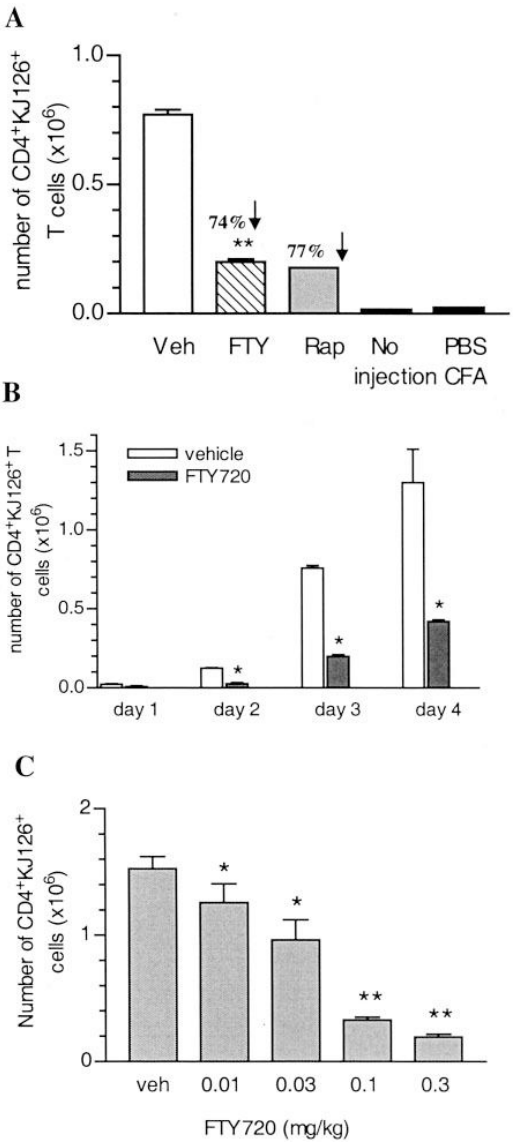

FIGURE 1. Reduced expansion of the number of Ag-specific T cells by FTY720 in DLN of Ag-challenged mice. Splenocytes from DO11.10 mice were adoptively transferred into unirradiated BALB/c mice by i.v. injection (3×10^7/mouse). On the following day the BALB/c recipients were treated with rapamycin (1 mg/kg i.p.; *A*) or FTY720 (0.5 mg/kg orally in *A* and *B*, and various doses in *C*). After 4 h, mice were given footpad injections of 100 μg of OVA protein or PBS emulsified in same volume of CFA. FTY720 (FTY) and rapamycin (Rap) were given daily until 1 day before harvest. Draining popliteal nodes were harvested after 3 days of Ag challenge (*A* and *C*) or after 1, 2, 3, or 4 days of Ag challenge (*B*) and then stained with CD4-allophycocyanin and KJ126-PE. The percentage of $CD4^+KJ126^+$ cells in the DLN was determined by flow cytometry and multiplied by the total number of DLN cells to obtain the absolute number of $CD4^+KJ126^+$ cells. *A*, The number of $CD4^+KJ126^+$ T cells was reduced by 74% with FTY720 and by 77% with rapamycin treatment compared with the vehicle control after 3 days of Ag challenge. The expansion of $CD4^+KJ126^+$ cells was 74% less (**, $p < 0.005$; $n = 4$) with FTY720 and 77% less with rapamycin treatment on day 3 after Ag challenge. The numbers of $CD4^+KJ126^+$ cells from mice with no injection or with PBS-CFA are also shown. One of eight comparable experiments is shown. *B*, The number of $CD4^+KJ126^+$ cells in FTY720-treated mice was reduced by 64% on day 1, 78% on day 2, 74% on day 3, and 68% on day 4 after Ag challenge compared with the vehicle controls (*, $p < 0.05$ for days 2, 3 and 4; $n = 4$). One of two comparable experiments is shown. *C*, The expansion of $CD4^+KJ126^+$ cells was inhibited by 17, 37, 78, or 87% with 0.01, 0.03, 0.1, or 0.3 mg/kg FTY720, respectively. (*, $p < 0.05$; **, $p < 0.005$; $n = 5$). One of two comparable experiments is shown. Values indicate the mean ± SEM.

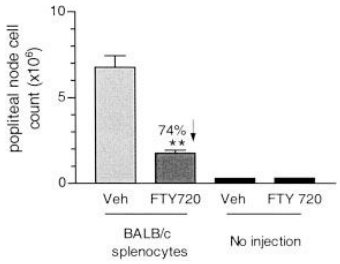

FIGURE 2. Reduced expansion in the number of DLN cells by FTY720 in alloantigen-challenged mice. FTY720 (0.5 mg/kg/day) was administered orally to C57BL/6 mice. Four hours later mice were given footpad injections of 1.5×10^7 BALB/c splenocytes. The draining popliteal nodes were harvested 3 days after alloantigen challenge and counted by hemocytometer. The expansion of LN cells was inhibited by 74% (**, $p < 0.005$; $n = 4$). No alloantigen injection control was included. One of three comparable experiments is shown.

After 3 days of Ag stimulation, the total number of DLN cells in FTY720-treated mice was significantly less than that in vehicle-treated mice (data not shown). Although the percentages of $CD4^+KJ126^+$ cells in vehicle- and FTY720-treated animals were similar (data not shown), the absolute number of $CD4^+KJ126^+$ cells in FTY720-treated mice was 74% less compared with that in vehicle-treated groups (Fig. 1*A*). Treatment with rapamycin, a cell cycle blocker, also reduced $CD4^+KJ126^+$ cells by 77% in the DLN (Fig. 1*A*). To investigate the possibility that FTY720 simply alters the kinetics of the immune response in the DLN, we conducted a time-course study to examine T cell expansion in the DLN after 1, 2, 3, or 4 days of Ag stimulation. As shown in Fig. 1*B*, for each day examined, the number of $CD4^+KJ126^+$ cells in the DLN of FTY720-treated mice was less (ranging from 64–78%) compared with that in the vehicle controls. A similar reduction was observed with FTY720 treatment on day 7 after Ag challenge in a separate experiment (data not shown). Furthermore, the number of Ag-specific T cells was reduced by FTY720 in a dose-dependent fashion, with a 50% inhibitory dose between 0.03 and 0.1 mg/kg (Fig. 1*C*).

We also locally introduced another type of Ag, alloantigen and examined the T cell response in DLN after FTY720 treatment. C57BL/6 mice were treated daily with vehicle or FTY720 (0.5 mg/kg orally), with the first dose given 4 h before footpad injection of 1.5×10^7 BALB/c splenocytes. Three days after alloantigen stimulation the number of DLN (draining popliteal node) cells was increased to $6.76 \pm 0.68 \times 10^6$ (Fig. 2). However, with FTY720 treatment the number of DLN cells was only increased to $1.77 \pm 0.17 \times 10^6$, which was 74% less compared with the vehicle control value. Without alloantigen stimulation, 3 days of FTY720 treatment did not significantly change the number of popliteal node cells (Fig. 2). In conclusion, we found that T cells respond to Ag or alloantigen stimulation in DLN of FTY720-treated mice, but the final number of responding T cells in DLN is significantly less after FTY720 treatment.

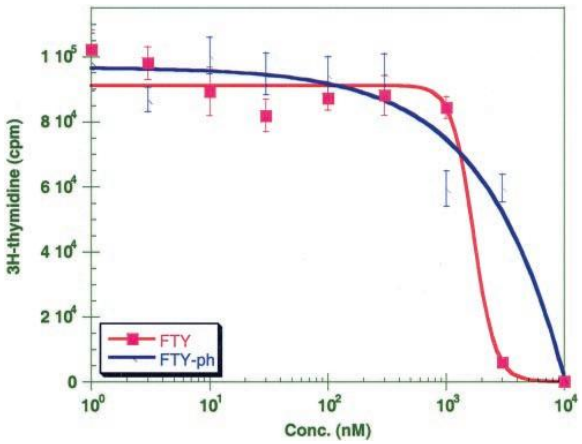

FIGURE 3. In vitro T cell proliferation. Irradiated splenic cells from C57BL/6 mice (100 μl at 5×10^6/ml) were cultured with BALB/c splenic cells (100 μl at 5×10^6/ml) in RPMI 1640 medium. Cells were treated with various doses of FTY720 or FTY720-phosphate. Three days later cells were pulsed with [^{3}H]thymidine, and the incorporation of [^{3}H]thymidine was determined after 16–18 h of pulsing. One of two comparable experiments is shown.

T cell proliferation in a MLR in vitro

To investigate whether T cell proliferation was inhibited by FTY720, we examined in vitro T cell responses in a MLR. Upon stimulation with the alloantigen provided by irradiated C57BL/6 splenic cells, BALB/c T cells were activated and proliferated, as judged by thymidine incorporation (Fig. 3). FTY720, at doses up to 1 μM, had no effect on thymidine incorporation of BALB/c T cells. At higher doses (>1 μM), FTY720 caused a dramatic decrease in thymidine incorporation, but we also observed a high percentage of TUNEL-positive apoptotic T cells (data not shown), suggesting that the decrease in thymidine incorporation was due to the cytotoxicity of FTY720 (6). We further evaluated FTY720-phosphate, the active FTY720 metabolite that acts as a full agonist for the S1P receptors (13), in this proliferation assay. We found that FTY720-phosphate had no significant effect on T proliferation at doses up to 1 μM (Fig. 3). The blood concentration of FTY720-phosphate required to cause lymphopenia in vivo is several orders of magnitude less than 1 μM. Therefore, we conclude neither FTY720 nor its active metabolite interferes with T cell proliferation in vitro.

In vivo T cell proliferation analyzed by BrdU incorporation

In vivo T cell proliferation requires interaction of T cells and APC in the lymph node microenvironment. We examined in vivo T cell proliferation by injecting BrdU i.p. 2 days after OVA CFA injection in the DO11.10 adoptive transfer model described in Fig. 1. On the following day DLN were collected and stained with CD4 and KJ126 Abs for tracking Ag-specific T cells. In addition, cells that incorporated BrdU in vivo were detected by anti-BrdU Ab. Again, we found that the number of $CD4^+KJ126^+$ T cells was significantly less with FTY720 treatment, as shown in Fig. 1*A*. BrdU-incorporated cells were analyzed on the gated $CD4^+KJ126^+$ population. As shown in Fig. 4, 54.6 $\pm$ 1.2% of $CD4^+KJ126^+$ cells incorporated BrdU in the vehicle-treated group. FTY720 treatment (0.5 mg/kg/day) resulted in a modest increase in the percentage of $CD4^+KJ126^+$ cells that were BrdU positive ($p < 0.005$). However, since the number of $CD4^+KJ126^+$ cells in DLN was dramatically less after FTY720 treatment (Fig. 1), the absolute number of $CD4^+KJ126^+$ cells that incorporated BrdU was decreased by FTY720 treatment (data not shown).

In vivo T cell proliferation analyzed by CFSE fluorescence intensity

We next used CFSE to obtain information on the number of cell divisions in vivo. DO11.10 splenocytes were labeled with CFSE before adoptive transfer to BALB/c mice. FTY720 (0.5 mg/kg orally) and rapamycin (1 mg/kg i.p.) were given 4 h before Ag challenge and then daily until 1 day before harvest. DLN and non-DLN (contralateral popliteal node) were collected after 1, 2, or 3

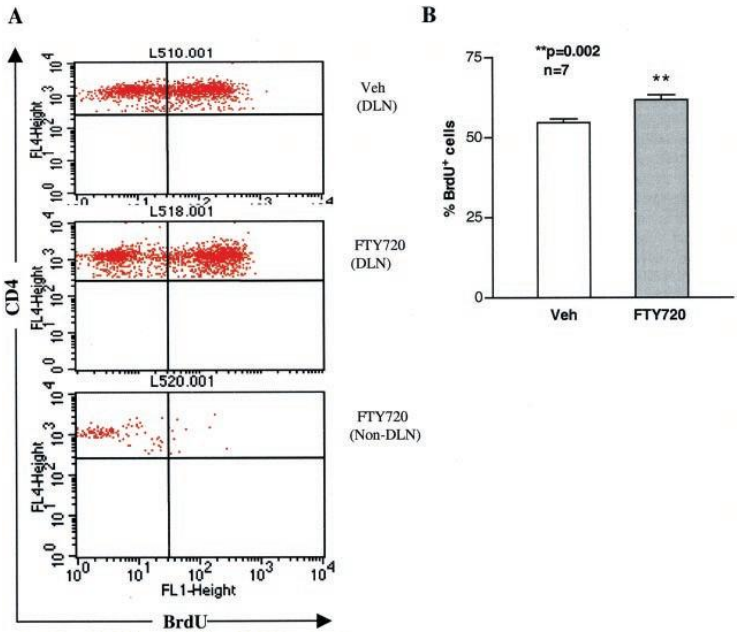

FIGURE 4. In vivo T cell proliferation analyzed by BrdU incorporation. DO11.10 splenocytes were adoptively transferred to BALB/c mice. The recipients were administered vehicle (veh) or FTY720 (0.5 mg/kg/day) and then challenged with OVA CFA in the footpad as described in Fig. 1. BrdU (1 mg) was injected to mice after 2 days of Ag challenge. On the following day the DLN or the contralateral popliteal node (Non-DLN) was harvested and stained with CD4-allophycocyanin, KJ126-PE, and anti-BrdU-FITC. BrdU-incorporated cells were analyzed after gating on $CD4^+KJ126^+$ cells. The *upper right quadrant* represents the percentage of $CD4^+KJ126^+$ cells that incorporated BrdU (*A*), which was then quantified as shown in *B*. One of two comparable experiments is shown.

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