Supplementary Figure 1

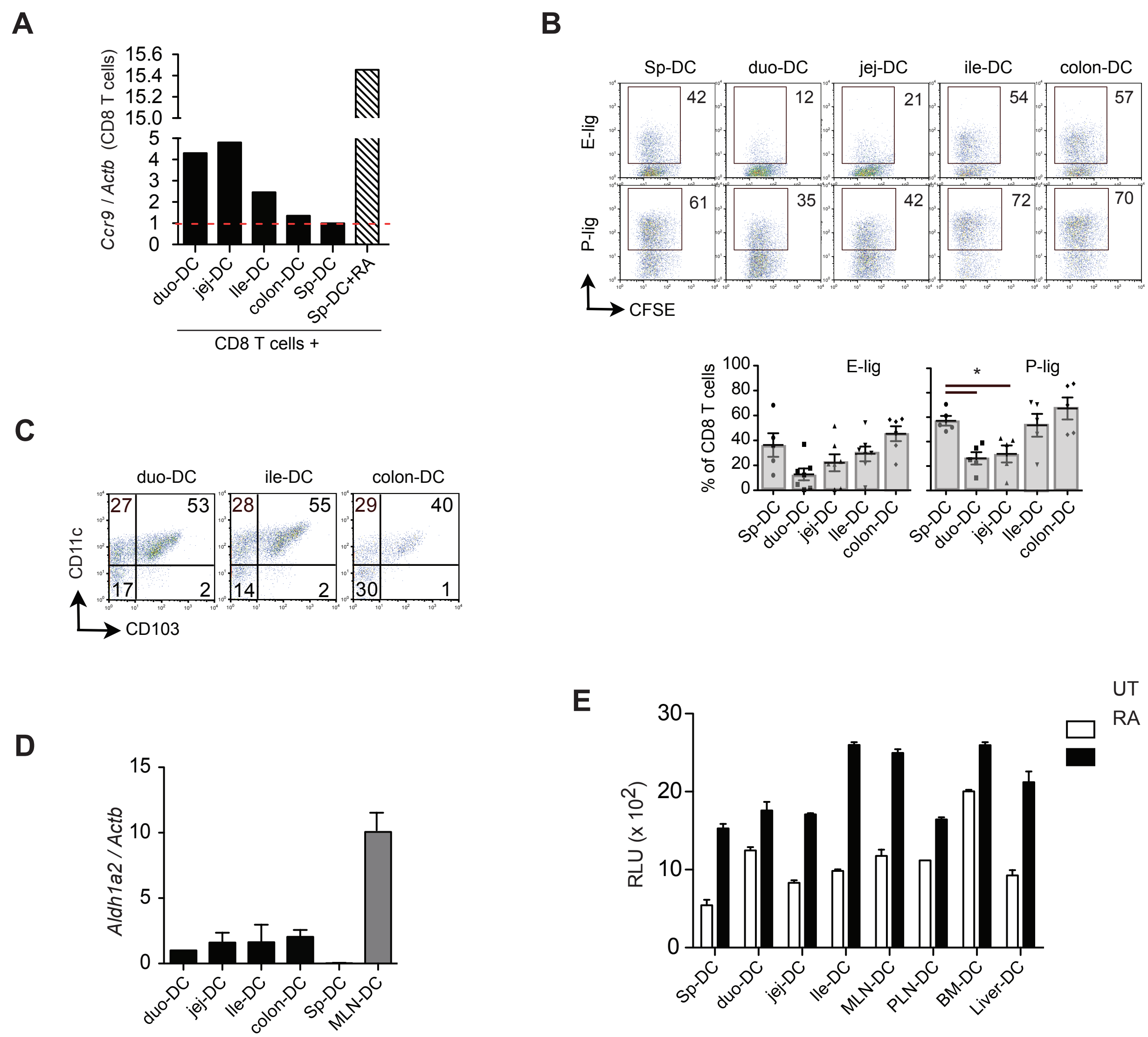

Fig. S1. (**A-B**) CD8 T cell were activated with Sp-DC, PP-DC from duodenum (duo), jejunum (jej), ileum (ile) or colon LP-DC and analyzed after 4 days. (**A**) Expression of *Ccr9* mRNA in activated T cells. As positive control, 10 nM RA was supplemented to some co-cultures with Sp-DC. Graph is representative of two independent experiments. (**B**) Expression of P- and E-selectin ligands on activated T cells (n=5). (**C**) CD103 expression in LP-DC from duo, ile and colon. (**D**) *Aldh1a2* mRNA expression in PP-DC from duo, jej, ile and LP-DC from colon. Sp-DC and MLN-DC are shown as a reference (n=6). (**E**) DC from different tissues were isolated from DR5-luciferase mice and incubated for 24 h with or without 10 nM RA. After that, they were analyzed for their luciferase activity (n=2). Mean ± SEM, $^{*}p<0.05$

Supplementary Figure 2

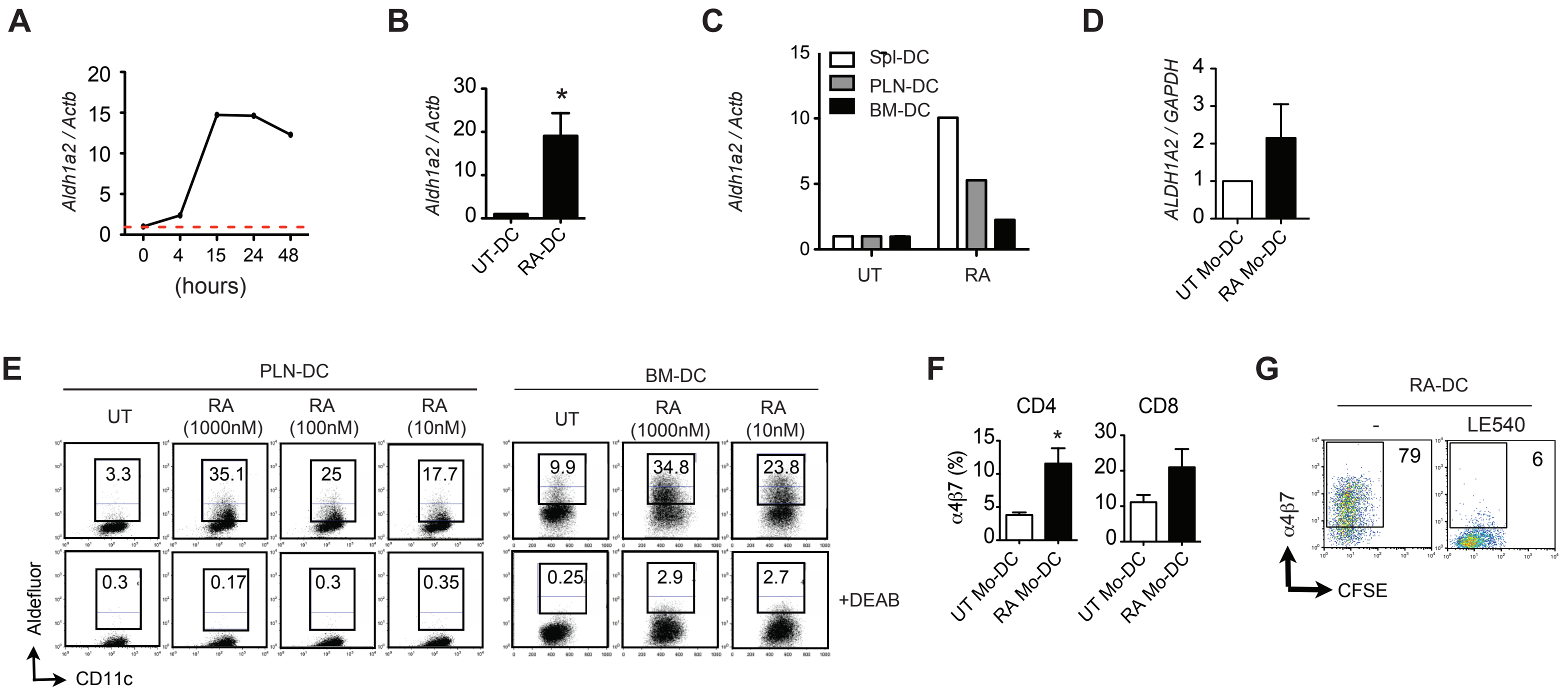

Fig. S2. (**A-B**) Sp-DC were treated with (RA-DC) or without (UT-DC) 100 nM RA. (A) Kinetics for *Aldh1a2* mRNA expression and (**B**) pooled data at 24 h (n=7). (**C**) Aldh1a2 mRNA levesl on Sp-DC, PLN-DC or BM-DC treated or not with RA (1000 nM). (**D**) Human monocytes were differentiated to DC (Mo-DC) and at day 6 were incubated for 24 hours with (RA) or without (UT) 100 nM RA. *ALDH1A2* mRNA expression in Mo-DC normalized respect to *GAPDH* mRNA (n=4). (**E**) PLN-DC or diferentiated Bone marroe-derived DC (BM-DC) were treated or not with different concentration of RA. Upon 24 h, RALDH activity was measure using Aldefluor on CD11c cells. One representative experiment out of 2. (**F**) Human monocytes were differentiated as in (D). UT or RA Mo-DC were co-cultured with total human T cells activated with plate-bound anti-CD3 plus anti-CD28 antibodies. After 6 days, CD4 and CD8 T cells were analyzed for their expression of α4β7 (n=5). Mean ± SEM, $^*p<0.05$ (**G**) RA-DC were co-culture with CFSE-labeled naive P14 T cells in the presence or absence of 1 μM LE540. After 4 days, CD8 T cells were analyzed for their expression of α4β7.

Supplementary Figure 3

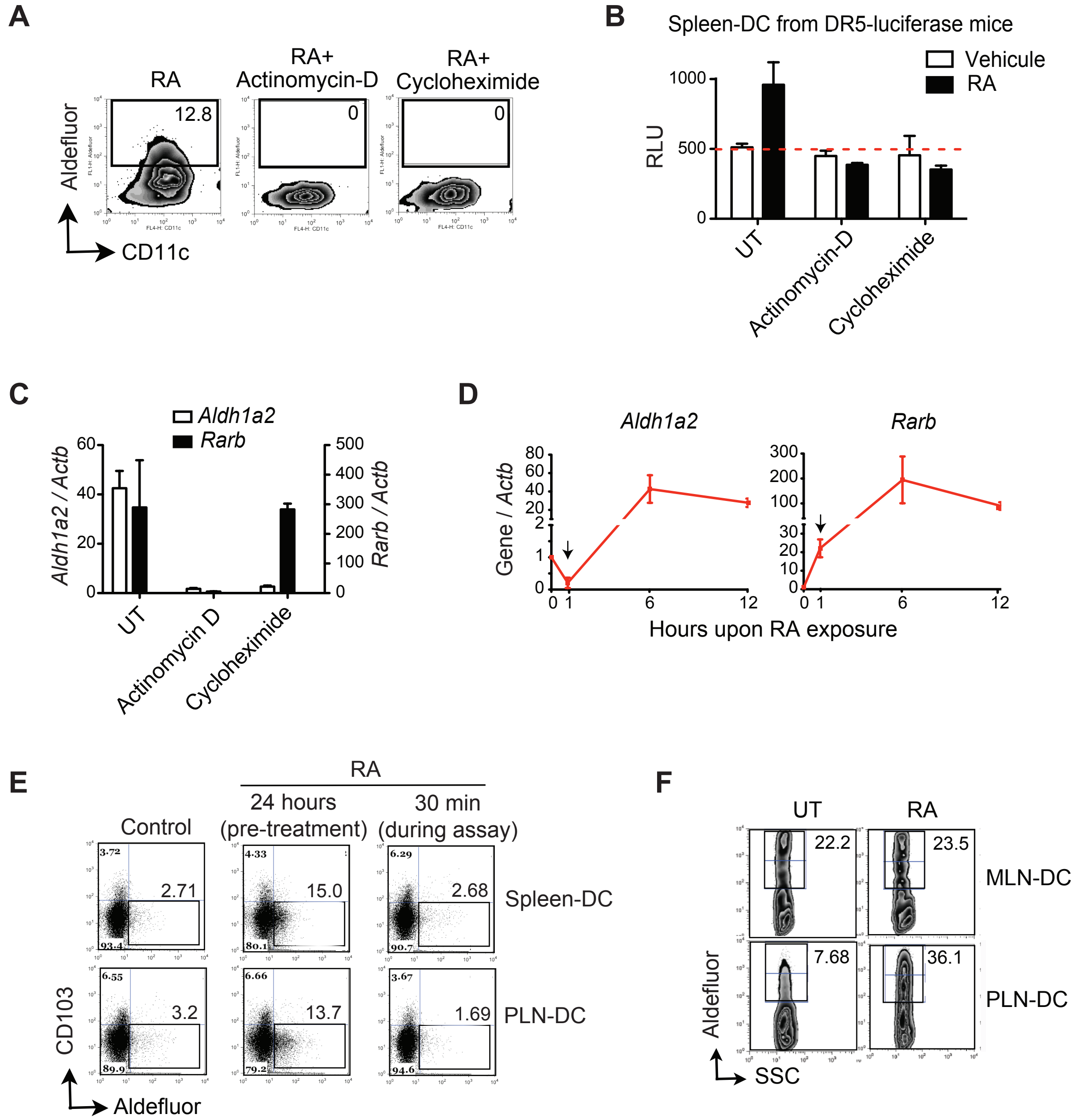

Fig. S3. (**A-D**) Spleen-DC from DR5-luciferase mice were treated or not with 100 nM RA and in the presence or absence of the transcription inhibitor actinomycin-D (1 µg/ml) or the translation inhibitor cycloheximide (10 µg/ml). After 20 hours the cells were assessed for their Raldh activity (Aldefluor staining) (**A**) and luciferase activity (**B**). *Aldh1a2* and *Rarb* mRNA were analyzed at either 5 hours (**C**) or at different time points (**D**). Mean ± range, (n=2). (**E**) Raldh activity in spleen-DC treated or not with RA for either 24 hours or 30 min (i.e., only during the Aldefluor assay). (**F**) Raldh activity in MLN-DC or PLN-DC from mice untreated or treated orally with RA (400 µg/day for 5 days).

Supplementary Figure 4

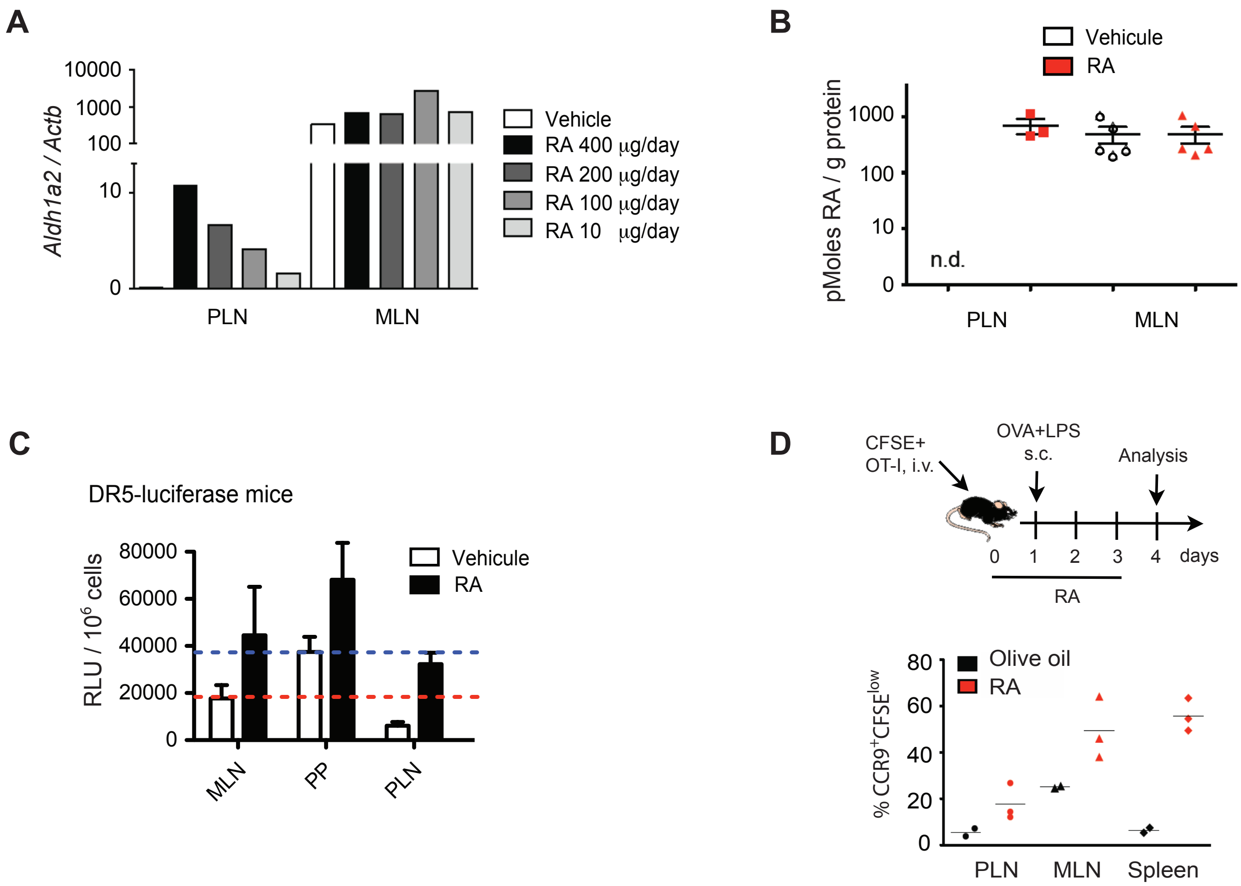

Fig. S4. (**A**) Wild type mice were orally treated with different concentration of RA (10-400 µg/day) for 4 days. PLN-DC and MLN-DCwere isolated at day 4 and analyzed for their expression of *Aldh1a2* mRNA. (**B-C**) Wild type mice (**B**) or DR5-luciferase mice (**B**) were treated with 400 µg/day RA or vehicle for 4 days (n=5 mice/group). (**A**) RA levels in PLN and MLN. (**B**) Luciferase activity in MLN, PP and PLN from DR5-luciferase mice. (**D**) Wild type Thy1.1+ congenic mice were treated with RA (400 µg/day for 3 days) or vehicule (olive oil) every day via oral gavage. At day 0 the mice were adoptively transferred with CFSE-labeled OT-I CD8 cells. At day 1 the mice were immunized with OVA (500 µg) + LPS (50 µg) s.c. After 3 days PLN, MLN and spleen were analyzed for CCR9 expression on proliferating Thy1.2+ CD8 T cells. (n=2-3). Mean ± SEM

Supplementary Figure 5

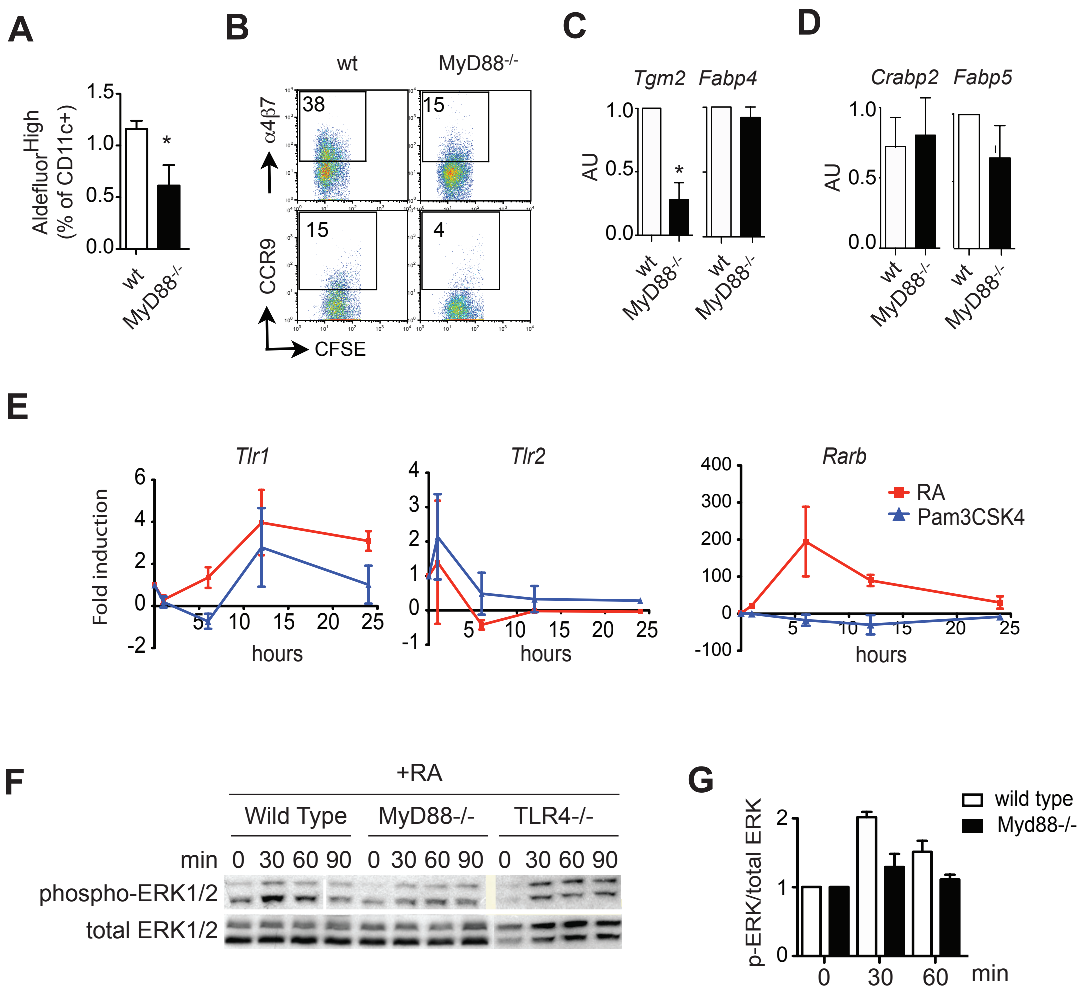

Fig. S5. (**A**) Wild type or MyD88$^{-/-}$ mice were supplemented orally with RA (400 µg/dose) every other day for 6 days. After that, PLN-DC were analyzed for Raldh activity (n=7). (**B**) Sp-DC from RA-supplemented wild type or MyD88$^{-/-}$ mice were used to activate naïve CD8 T cells. After 4 days T cells were analyzed for α4β7 and CCR9 expression. FACS plots show one experiment using DC pooled from 4 mice. (**C**) PP-DC from wild type or MyD88$^{-/-}$ mice were analyzed for their expression of *Tgm2* and *Fabp4* mRNA (n=7). (**D**) Spleen-DC from wild type or MyD88$^{-/-}$ mice were analyzed for their expression of *Crabp2* and *Fabp5* mRNA. (**E**) Kinetics of *Tlr1*, *Tlr2* and *Rarb* mRNA expression in spleen-DC upon RA or Pam3CSK4 treatment. (n=3). Mean ± SEM. (**F**) Wild type, MyD88$^{-/-}$ and TLR4$^{-/-}$ spleen-DC were treated with RA for 0, 30, 60 and 90 minutes. Cell lysates were analyzed by Western blot for ERK1/2 phosphorylation and total ERK1/2. (**G**) Semi-quantitative analysis of p-ERK1/2 and total ERK1/2 normalized versus untreated samples (n=2). Mean ± SEM. *p<0.05

Supplementary Figure 6

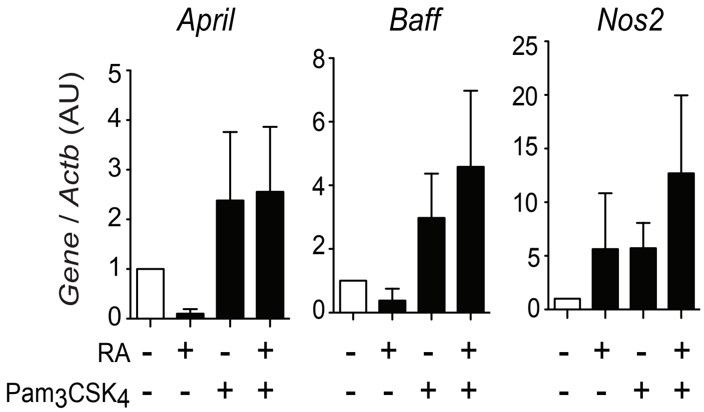

Fig. S6. Sp-DC were incubated for 24 h with or without 100 nM of RA, Pam_3CSK_4 (0.5 μg/ml) or both and then analyzed for their expression of *April*, *Baff* and *Nos2* mRNA (n=3).

Supplementary Figure 7

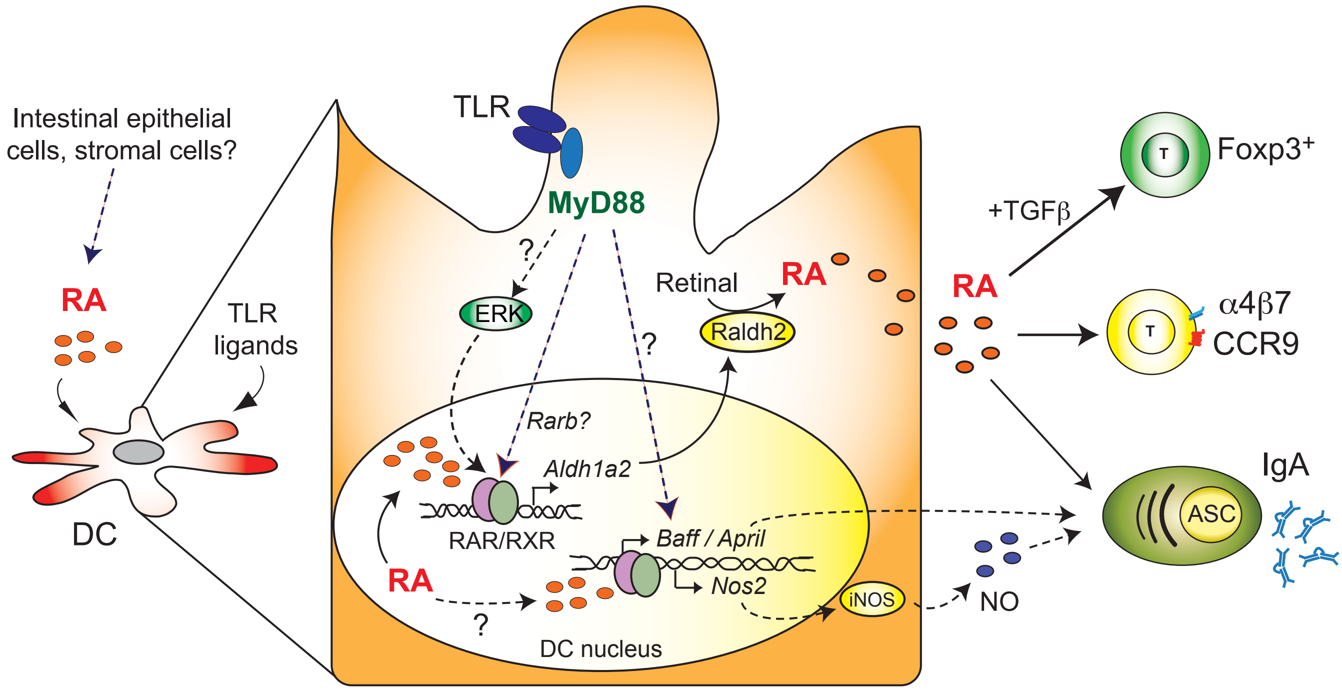

Fig. S7. Model for RA-mediated DC education. RA acts on DC via RAR-RXR nuclear receptors to induce *Aldh1a2* expression (encoding Radh2). Raldh2 metabolizes retinal into RA, which induces gut-homing receptors on T cells. In addition, RA potentiates the differentiation of IgA-ASC and Foxp3+ T_{REG}. RA also induces *Nos2* (encoding iNOS) in DC, hence boosting the induction of IgA-ASC by increasing nitric oxide (NO). MyD88 is required for RA-mediated DC education, probably by modulating *Rarb* expression (encoding RARβ) and/or by activating ERK/MAPK, which is also needed for RA-mediated effects on DC.

Supplemental Text-1

Consistent with a physiological role of RA in DC education, the proximal-to-distal retinoid gradient tightly correlated with DC imprinting abilities. DC from duodenum and jejunum induced higher levels of gut-tropic and Foxp3$^+$ T cells as compared to DC from distal intestinal segments. Since CCL25 (CCR9-ligand) also follows a proximal-to-distal gradient [1], it is tempting to speculate that DC from duodenum/jejunum might be preferentially involved in the establishment of oral tolerance by transporting food-borne antigens to the MLN where they would induce Foxp3$^+$CCR9$^+$ T_{REG} that will preferentially migrate to proximal intestinal segments, hence preventing undesired immune responses to innocuous antigens as soon as they have access to the intestinal mucosa.

Supplemental Text-2

In support of this possibility, it has been described that an IEC line promotes gut-homing imprinting when co-cultured with T cells activated with extra-intestinal DC [2]. Another study showed that IEC can condition extra-intestinal DC to induce T_{REG} *in vitro*, an effect that was partially dependent on RA and TGF-β [3]. However, since there are no studies assessing the specific contribution of IEC-derived RA in gut-associated DC education *in vivo*, the physiological relevance of IEC in this context remains to be determined.

Although our data show that RA readily upregulates *Aldh1a2* mRNA (encoding Raldh2), RA did not consistently induce *Aldh1a1* mRNA (encoding Raldh1) in extra-intestinal DC (data not shown), suggesting that the induction of Raldh1 and Raldh2 isozymes is differentially regulated. These considerations notwithstanding, it has been reported that gut-associated DC mainly express Raldh2 [4] and that this isozyme is about 5-10 times more efficient at synthesizing RA as compared to Raldh1 [5]. In addition, although RA has been shown to induce enzymes involved in the first step of its biosynthesis from retinol to retinal [6], other studies have shown that it actually inhibits the expression of

Raldh enzymes in non-immune cells (including IEC), thus blocking the final step in the synthesis of RA [7-10]. By contrast, our data clearly show that RA induces a positive feedback loop in DC, which is additionally translated in functional effects on lymphocyte imprinting. Thus, whether RA promotes a positive or a negative feedback loop on its own synthesis seems to depend, at least in part, on the specific Raldh isoform and on the particular tissue/cell type analyzed.

Supplemental Text-3

Whereas the exact mechanism of how MyD88 controls RA effects on DC remains to be fully clarified, our results indicate that RARβ might be involved in RA-mediated DC education and that the expression of RARβ depends on MyD88 signaling. Of note, RARβ is also expressed in gut-associated follicular DC (FDC) and its expression depends on RA [11], suggesting that RA also modulates the expression of this RAR isoform.

Besides modulating DC to synthesize RA and to induce gut-tropic T cells, RA was also required *in vivo* to confer gut-associated DC with IgA-inducing capacity and it synergized with TLR stimulation to confer extra-intestinal DC with IgA-inducing potential. It is likely that RA might influence DC via different mechanisms, including RA production itself, which can directly acts on B cells to promote differentiation of IgA-ASC [12]. In addition, RA can induce TGFβ synthesis by DC [13] and we found that TLR1/2 stimulation or RA can induce *Nos2* mRNA (encoding iNOS) in DC, which might additionally contribute to the induction of IgA-ASC [14]. In line with our observations, it has been described that RA can potentiate iNOS induction *in vivo* [15].

Materials & Methods

Mice

OT-1xRAG2$^{-/-}$, P14xTCRα$^{-/-}$, C57BL/6, and C57BL/6/Thy1.1^{+} mice were purchased from Taconic (Germantown, NY). MyD88$^{-/-}$ mice [16] were provided by Dr. Nir Hacohen (Massachusetts General Hospital, Boston, MA). DR5-luciferase mice [17] were provided by Dr. Rune Blomhoff (Cgene AS, Oslo, Norway). LRAT$^{-/-}$ mice [18] were provided by Dr. William Blaner (Columbia University, NY, USA). Mice were maintained in SPF/VAF animal facilities at Massachusetts General Hospital (MGH) and used in accordance with the guidelines from the Subcommittee on Research Animal Care at MGH and Harvard Medical School.

Reagents

Nuclear receptor agonists: Pan-RAR-agonist all-*trans* RA, Pan-RAR/Pan-RXR-agonist 9-*cis* RA, Pan-RAR-agonist 13-cis RA and the PXR-agonist Lithocholic acid, actinomycin-D and cycloheximide were purchased from Sigma (St Louis, MO); LXR-agonist TO901317 (Cayman, Ann Arbor, MI); PPARβ/δ-agonist GW0742 (Tocris, Ellisville, MI); AHR-agonist 2-(19H-indole-39-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) (Tocris, Ellisville, MI); PPARγ-agonist Rosiglitazone (Cayman, Ann Arbor, MI); RXR-agonists PA024 and HX630; and RARα/β-agonist Am80 were provided by Dr. Hiroyuki Kagechika (Tokyo Medical and Dental University, Japan); Raldh inhibitor 4-(diethylamino)-benzaldehyde (DEAB) (Stemcell, Vancouver); RARβ-antagonist LE540 (Wako Chemicals USA, Richmond, VA) was dissolved in DMSO or ethanol (1 mM stocks) and used at 1 μM final concentration. The following mAb used to label murine cells were purchased from BD Biosciences (San Jose, CA): anti-α4b7 (DATK32), anti-B220 (RA3-6B2), anti-CD3 (17A2), anti-CD19 (1D3), anti-Pan-NK (DX5), anti-Ly-76 (Ter-119), anti-CD11c (HL3), anti-CD103 (M290) and anti-IgA (C10-1). Anti-mouse CCR9 (CW-1.2) was from eBioscience (San Diego, CA). MAb used to label human cells: anti-CD4 (clone SK3) and anti-CD8 (clone SK1) were from BD Biosciences (San Jose, California). Anti human-α4β7 (ACT-1) was from Millennium Pharmaceuticals (Cambridge, MA). TLR1/2 ligand (Pam_3CSK_4) was from InvivoGene (San Diego, CA). Pharmacological inhibitors for P38/MAPK (SB203580), ERK1/2/MAPK (U0126), JNK/MAPK (SP600125) and NF-κB (SN50) were from Calbiochem (EMD Biosciences, San Diego, CA) and have been described [19]. The ERK1/2-inhibitor PD0325901 used for *in vivo* experiments [20] was purchased from Stemgent (Cambridge, MA). The cell tracers CFSE (Carboxyfluorescein diacetate, succinimidyl ester) and CMTMR (5-(and-6)-(((4-chloromethyl) benzoyl) amino) tetramethylrhodamine) were from Molecular Probes (Invitrogen, USA). LCMV$gp_{33–41}$ and ovalbumin SIINFEKL peptide were purchased from New England Peptides (Invitrogen, USA).

Mouse DC isolation and conditioning

C57BL/6 mice were injected subcutaneously with B16 melanoma cells secreting Flt3-L [12, 21]. After 12–17 days, the mice were euthanized and single-cell suspensions were generated by digestion with Liberase® TL (0.15mg/ml, Roche, Indianopolis, USA) and DNase 1 (325 Units/ml, Sigma-Aldrich) dissolved in HBSS medium without serum. DCs were immunomagnetically isolated by a first round of negative selection using MAbs to CD3, CD19, Pan-and NK, and goat anti-rat IgG microbeads (Miltenyi Biotec) and a second round of positive selection using CD11c magnetic beads (Miltenyi Biotec). DC (>98% $CD11c^+$) were treated for 24 hours with the indicated ligands, washed and used for co-culture with T and/or B cells, Aldefluor staining or RNA extraction. For co-culture with naïve CD8 T cells from TCR transgenic P14xTCR$\alpha^{-/-}$ or OT-1xRAG$2^{-/-}$ mice, DC were pulsed for 2 h with 100 nM LCMV$gp_{33–41}$ or ovalbumin SIINFEKL peptide, respectively, washed and used immediately.

Lymphocyte/DC isolation and cocultures

DC and naïve T cells were isolated and co-cultured as described [21]. Naïve P14 CD8 T cells were purified from splenocytes after RBC lysis in ACK buffer by negative selection, using mAbs to B220, I-A/I-E (2G9), CD4 (H129.19), CD19, Pan-NK, Ly-76 (Ter-119), and Ly-6G (Gr-1) followed by goat anti-rat IgG microbeads. $1x10^5$ CFSE-labeled naïve T cells were cocultured with peptide-pulsed DC in a 1:1 ratio in flat bottom 96-well plates (Falcon, BD Biosciences). For CFSE labeling, T cells were resuspended at 10^7 cells/ml in DMEM + 1% FBS + 20 mM Hepes, incubated with 2.5 mM CFSE for 20 min at 37ºC and then washed using an FBS gradient.

Naïve B cells were purified from spleens by negative selection using anti-CD43 microbeads (Miltenyi Biotec, >90% $B220^+$ cells) [12]. $1x10^5$ B cells were activated with 10 µg/ml anti-mouse IgM (Jackson Immunoresearch, USA) plus IL-5 (5ng/ml) either alone or plus Spleen-DC pre-treated or not with 100 nM RA (1:1 B cell:DC ratio). 4-5 days later, activated $B220^{Int}$ B cells/ plasmablasts were analyzed by flow cytometry for intracellular IgA expression and for IgA in the culture supernatant [12].

In vivo RA and PD0325901 treatment

C57BL/6 mice were treated with RA (400 µg/dose) or vehicle (olive oil) by oral gavage three times every other day. PD0325901 was dissolved in DMSO (50 mg/ml stock) and then diluted in water containing 0.05% hydroxypropyl-methylcellulose and 0.02% Tween 80 (final concentration: 2.5 mg/ml PD0325901) [20]. 250 µl/dose (25 mg/kg) were administered by oral gavage twice (day 0 and 3). Animals treated with either RA or PD0325901 were sacrificed one day after the last dose and $CD11c^+$ positive cells were purified from MLN, PLN and spleen by using magnetic beads (>96% $CD11c^+$). Raldh activity and/or mRNA levels were measured in the isolated DC by using Aldefluor® assay or TaqMan qPCR, respectively.

Retinoid measurements

Retinoid concentrations were assessed as described [22]. Briefly, tissue samples were homogenized in ground glass homogenizers (Kontes, size 22) in 0.5 to 1.0 mL saline (0.9% NaCl). All-*trans* RA was quantified by LC/MS/MS with APCI in positive ion mode on an API-4000 (Applied Biosystems). Retinol and retinyl esters were quantified by HPLC/UV on an Alliance 2690 (Waters). Retinoids in tissues are expressed as mol/g tissue.

Human DC differentiation and T cell co-culture

PBMCs from healthy donors (5-6x10^7) were cultured in RPMI 3% human serum for 1 h at 37°C. Adherent cells were then cultured in RPMI 10% FBS supplemented with GM-CSF (100 ng/ml; R&D Systems, Lauderdale, MN, USA). At day 6, differentiated (Mo-DC) were collected and conditioned with or without RA (100 nM, Sigma). At day 7, DC were analyzed by FACS, washed for co-culture or processed for RNA extraction. In some experiments, Mo-DC were co-cultured with enriched allogeneic CFSE-labeled T cells (Pan T cell isolation kit II, Miltenyi Biotec) in a 1:1 T:DC ratio and T cells were activated using plate-bound anti-CD3 (OKT3, eBioscience) plus anti-CD28 (CD28.6, eBioscience) (10 μg/ml each). After 5-7 days T cells were collected, stained for CD4, CD8 and α4β7 and then analyzed by FACS. In Foxp3 induction experiments Mo-DC were co-culture with allogeneic CD4 T cells (human CD4 isolation kit, Miltenyi Biotec) activated with anti-human CD3 (10 μg/ml), anti-human CD28 (1 μg /ml) and hTGF-β1 (2 ng/ml) for 4 days.

ELISA for IgA

Measurements of IgA in the culture supernatants was performed as described [12] using the ELISA Quantitation Kit for mouse and human IgA (Bethyl Laboratories, Montgomery, TX) according to the manufacturer's protocol.

Intracellular IgA labeling

Activated B cells were labeled with anti-B220 (RA3-6b2) and CD138 (281-2). After that, they were fixed and permeabilized using the CytoFix/CytoPerm kit (BD Biosciences, USA), labeled intracellularly with anti-IgA (C10-1) or a matched isotype control and analyzed by flow cytometry [12].

Aldefluor staining

Raldh activity was determined using the Aldefluor® assay (StemCell technology, Vancouver, Canada), as described [4]. Briefly, cells suspension (1x10^6 cells/ml) were incubated for 45 minutes at 37˚C in Aldefluor assay buffer containing activated Aldefluor substrate in the presence or absence of Raldh inhibitor diethylaminobenzaldehyde (DEAB). The cells were subsequently stained with specific antibodies, washed, resuspended in Aldefluor assay buffer and analyzed in a FACScalibur (BD Biosciences).

Quantitative PCR

Total RNA was isolated by using RNeasy (Qiagen) and then retrotranscribed with iScript cDNA synthesis kit (Bio-Rad, Hercules, CA). Quantitative PCR was performed using TaqMan PCR master mix (Applied Biosystems, Framingham, MA) using the following primers probes; *Aldh1a1* (Mm00657317_m1), *Aldh1a2* (Mm00501306_m1), *Rara* (Mm00436264_m1), *Rarb* (Mm01319674_m1), *Rarg* (Mm00441091_m1), *Rxra* (Mm00441182_m1), *Rxrb* (Mm00441193_m1), *Rxrg* (Mm00436410_m1), *Tgm2* (Mm00436980_m1), *Fabp5* (Mm00783731_s1), *CrabpII* (Mm00801693_g1), *Nos2* (Mm 01309901_m1) and *Actb* (NM_007393.1). For SYBR green we used the following primers: *Baff*-F: 5'AGG CTG GAA GAA GGA GAT GAG, *Baff*-R: 5' CAG AGA AGA CGA GGG AAG GG, *April*-F: 5' GGG GAA GGA GTG TCA GAG TG, *April*-R: GCA GGG AGG GTG GGA ATA C, *Tgfb1*-F: 5' TGG AGC AAC ATG TGG AAC TC, *Tgfb1*-R: 5' TGC CGT ACA

ACT CCA GTG AC, *GAPDH*-F: 5' CAT GGC CTT CCG TGT TCC TA, *GAPDH*-F: 5' GCG GCA CGT CAG ATC CA, Human *ALDH1A2*-F: 5' GGG CAG TTC TTG CAA CCA TGG AAT Human *ALDH1A2*-F: 5' TTT GAT GAC GCC CTG CAA ATC CAC, Human *ACTB-F*: AGG CCA ACC GCG AGA AGA TGA C Human *ACTB*-R: AGG TCC AGA CGC AGG ATG GCA T. The comparative Ct method was used to quantify transcripts that were normalized respect to *Actb* or *GAPDH*.

Western blot

Spleen-DC from wild type, MyD88$^{-/-}$ or TLR4$^{-/-}$ mice were stimulated with 100 nM RA for 30, 60 or 90 min. The cells were washed and homogenized in a lysis buffer containing 50 mM Tris (pH 8.0), 0.5% NP-40, 1 mM EDTA, 150 mM NaCl, 10% glycerol, 50 mM sodium fluoride, 10 mM sodium pyrophosphate,1 mM sodium orthovanadate, 1 mM phenylmethylsulfonyl fluoride, and a tablet of protease-inhibitor cocktail (Roche Diagnostics, Mannheim,Germany). Phosphorylated ERK1/2 (Thry202/Tyr204) or total ERK1/2, were detected with antibodies purchased from Cell SignalingTechnology (Beverly, MA). After stripping of anti-phospho-ERK1/2 Abs using Western blot stripping buffer (Pierce, Rockford, IL) the membranes were reprobed with anti-ERK1/2 Abs. Densitometric analyses were performed by calculating the band intensity ratio of phosphorylated-ERK1/2 to total-ERK1/2 using the software ImageJ (National Institute of Health, Bethesda, MD).

Competitive homing experiments

Thy1.2^{+} CD8 T cells were activated with UT-DC or RA-DC. After 4 days, activated T cells were labeled with 5 μM CFSE or 10 μM CMTMR, as described [12, 21]. Briefly, cells were resuspended at 1x10^{7}/ml, incubated with CFSE or CMTMR for 20 min at 37ºC, and washed in an FBS gradient. 1-2 x 10^{7} cells from each population were mixed in a 1:1 ratio and injected into recipient C57Bl/6 Thy1.1^{+}

mice. 18 h later the mice were euthanized, single cell suspensions were generated from spleen, MLN, intra-epithelial lymphocytes (IEL) or lamina propia (LP) from colon or small intestine (SI). Small bowel lamina propria cells were isolated after carefully dissecting out the Peyer's patches. Cells samples were incubated with anti-Thy1.2 and analyzed on a FACScalibur (BD Biosciences) by gating on viable $CD8^{+}Thy1.2^{+}$ cells. The homing index (HI) was calculated as: HI=[T cells activated with RA-DC]$_{tissue}$/[T cells activated with UT-DC]$_{tissue}$: [T cells activated with RA-DC]$_{input}$/[T cells activated with UT-DC]$_{input}$.

Statistical analysis

Unless specified otherwise, data are presented as mean ± SEM and were analyzed using GraphPad Prism Software 5.0b. Statistics were calculated using either unpaired *t* test when comparing two groups or ANOVA with Dunnett's or Bonferroni's post-hoc test when comparing more than 2 groups. Significance was set at $p < 0.05$.

References Supplemental Material

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