Journal club

Francesca Ronchi

July, 11th 2014

Activation of Gpr109a, Receptor for Niacin and the Commensal Metabolite Butyrate, Suppresses Colonic Inflammation and Carcinogenesis

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Immunity *40*, 128–139, January 16, 2014

Background

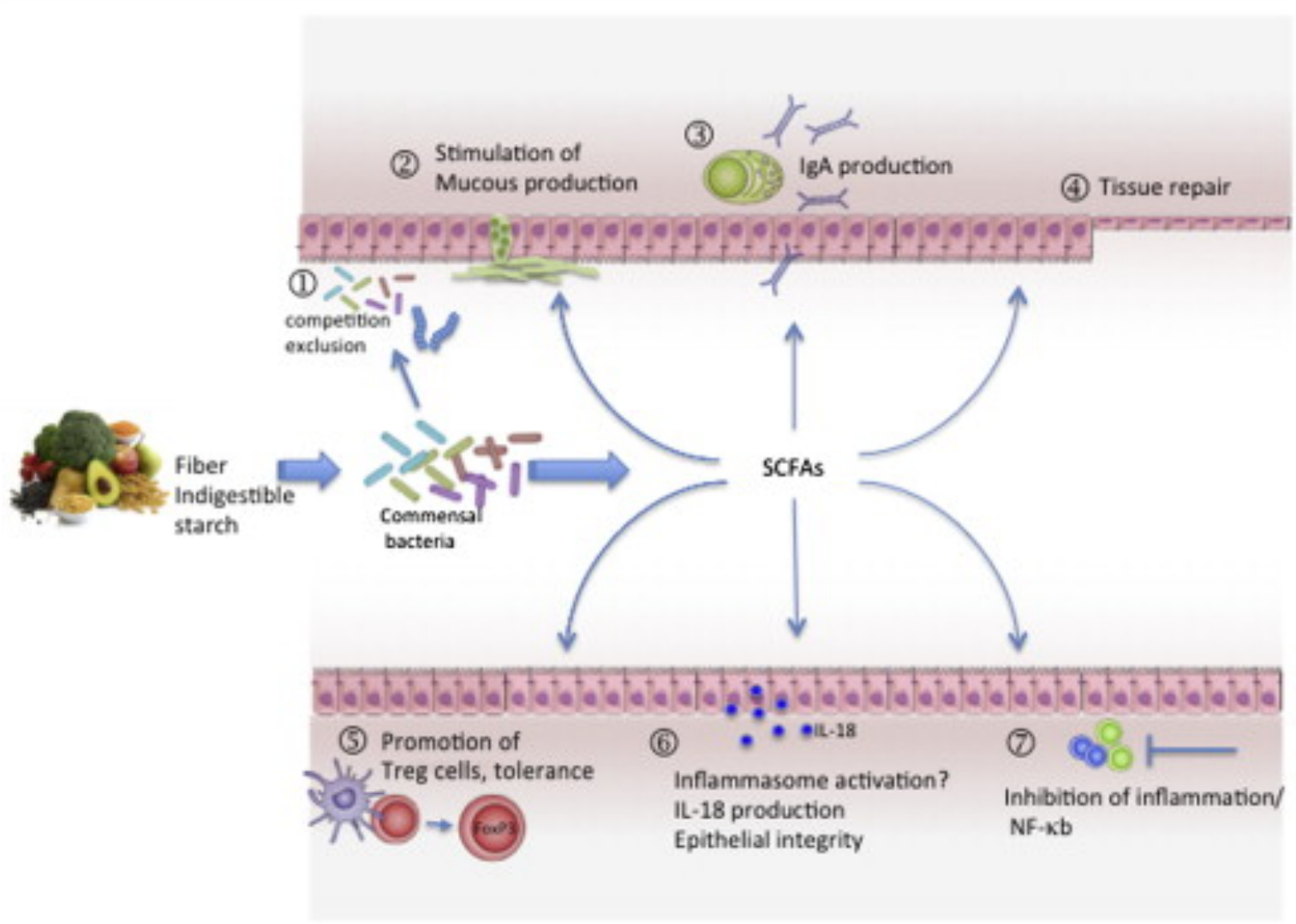


Figure 2. from 'Diet, Metabolites, and "Western-Lifestyle" Inflammatory Diseases'. Full Text Here: http://1.usa.gov/1nS6FVJ

Gpr109a Signaling Regulates Treg and IL-10-Producing CD4+ T Cell Frequency in the Colon

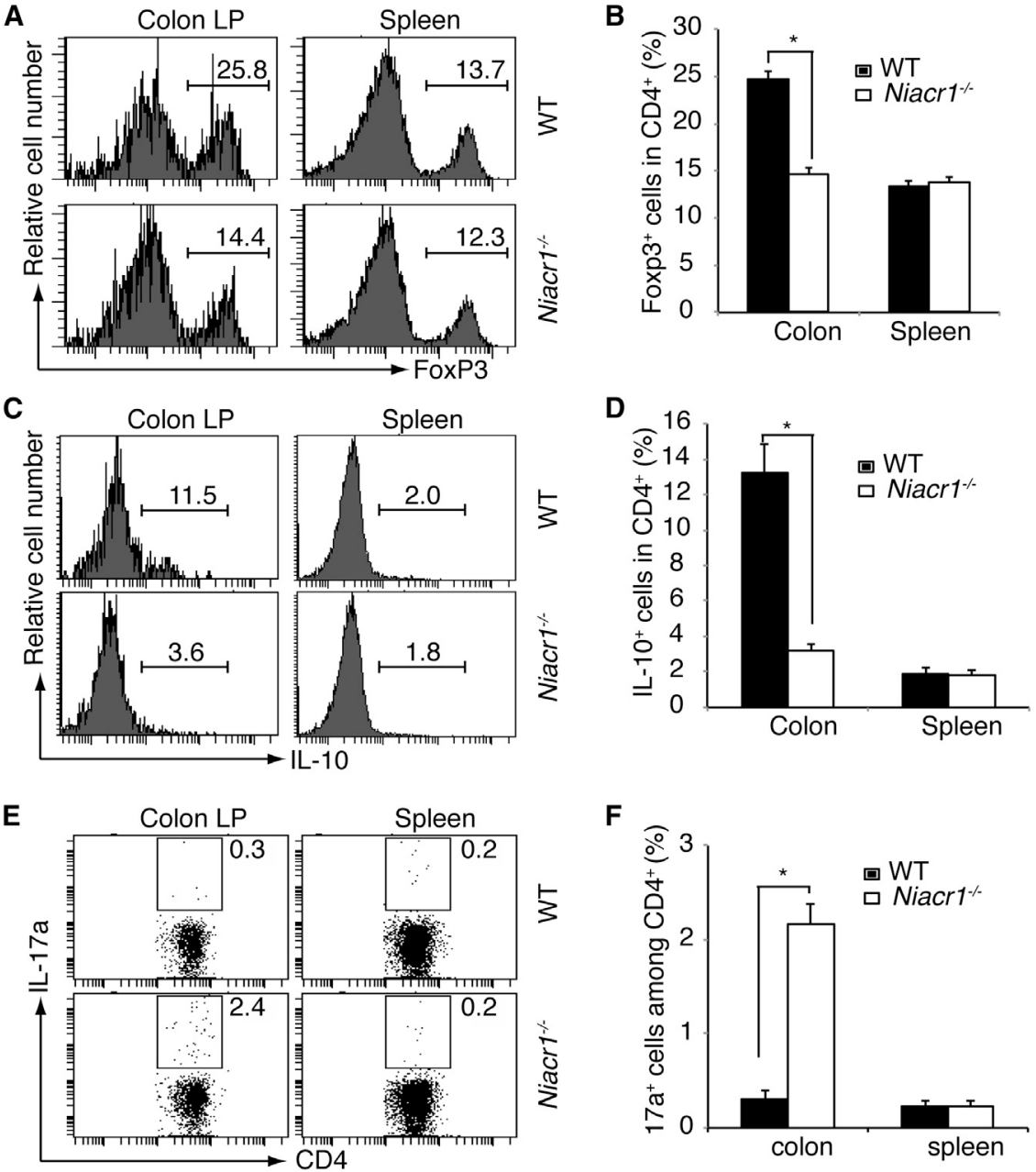


Fig.1

Colonic DCs and Macrophages from Niacr1$^{-/-}$ Mice Are Defective in Inducing Differentiation of Treg and IL-10-Producing CD4+ T Cells

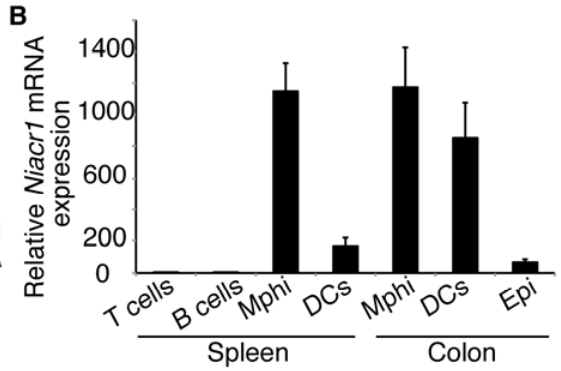
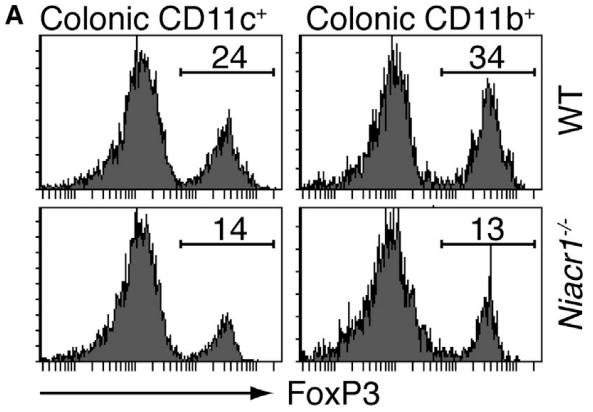
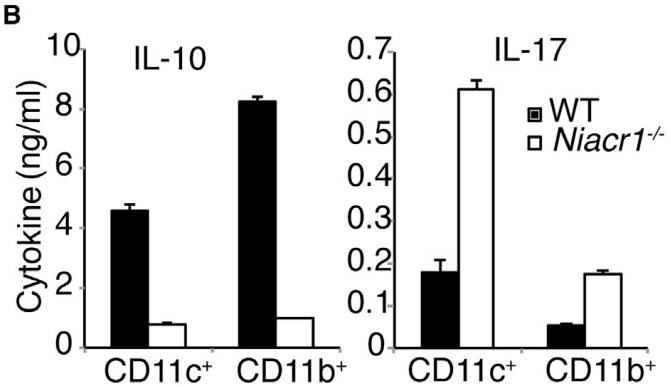


Fig.S2

OT-II CD4+CD25 T cell differentiated in the presence of TGF-b1, IL-2, and cognate peptide with colonic LP CD11c+ (CD45+I-Ab+ CD11c+) and CD11b+ (CD45+I-Ab+CD11b+) cells





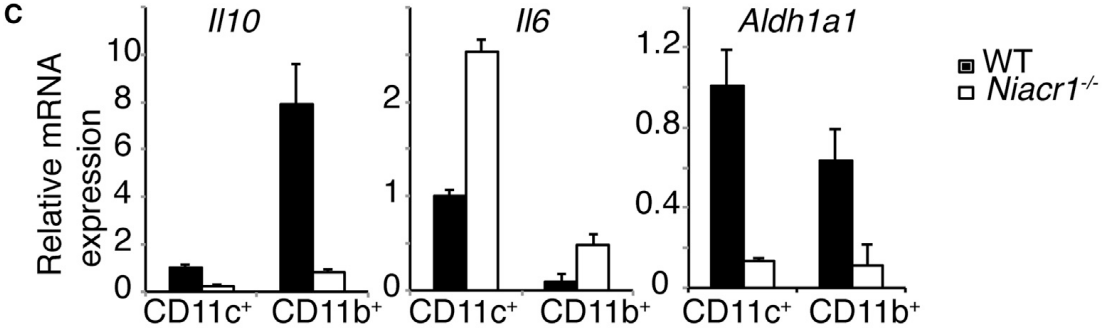


Fig.2

Butyrate- or Niacin-GPR109a Signaling Imparts Anti-inflammatory Phenotype on DCs and Macrophages

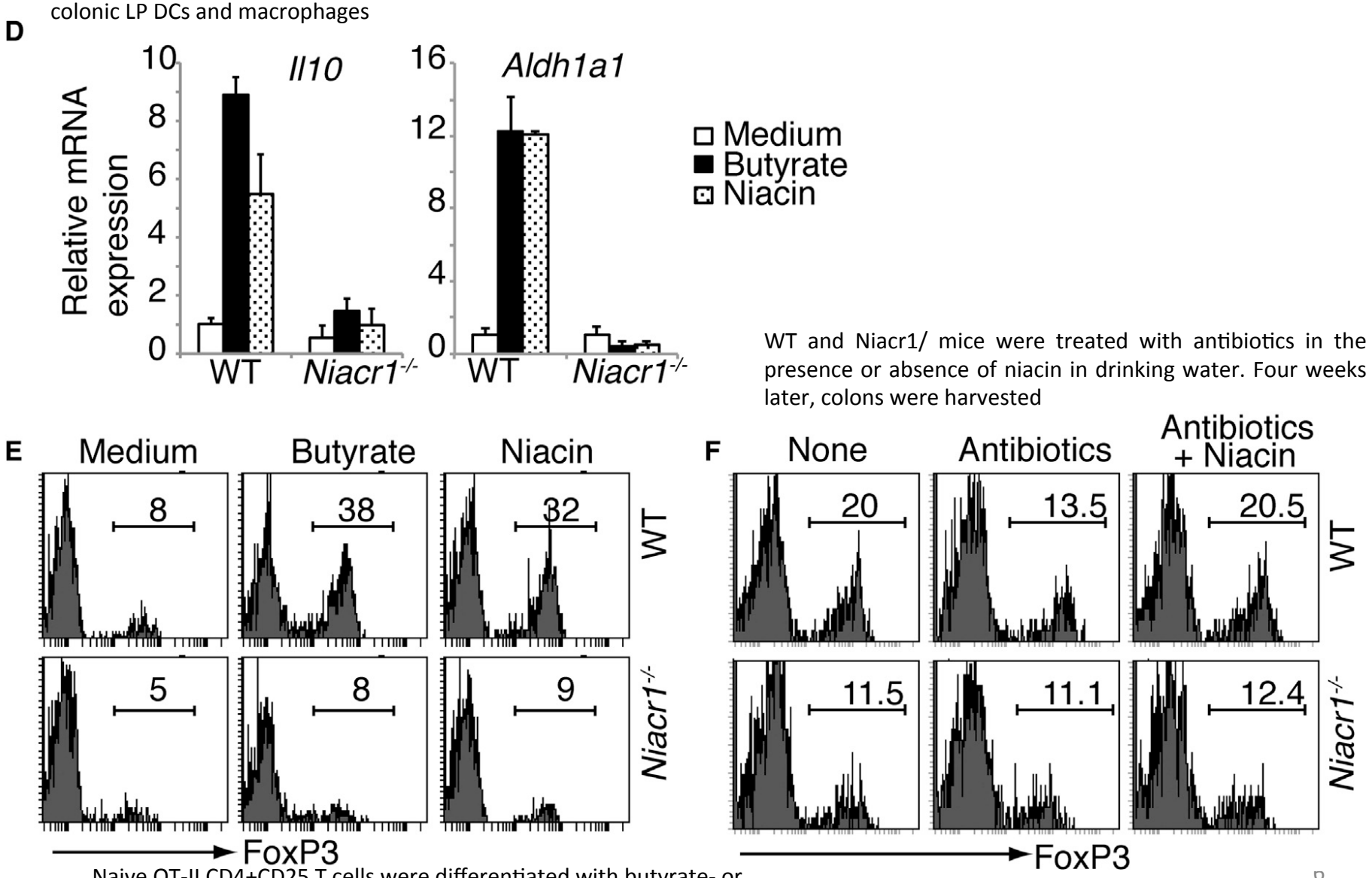
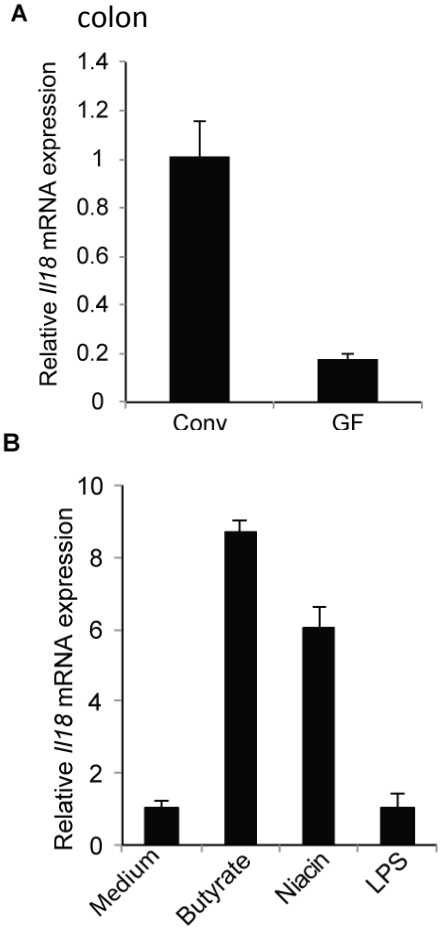


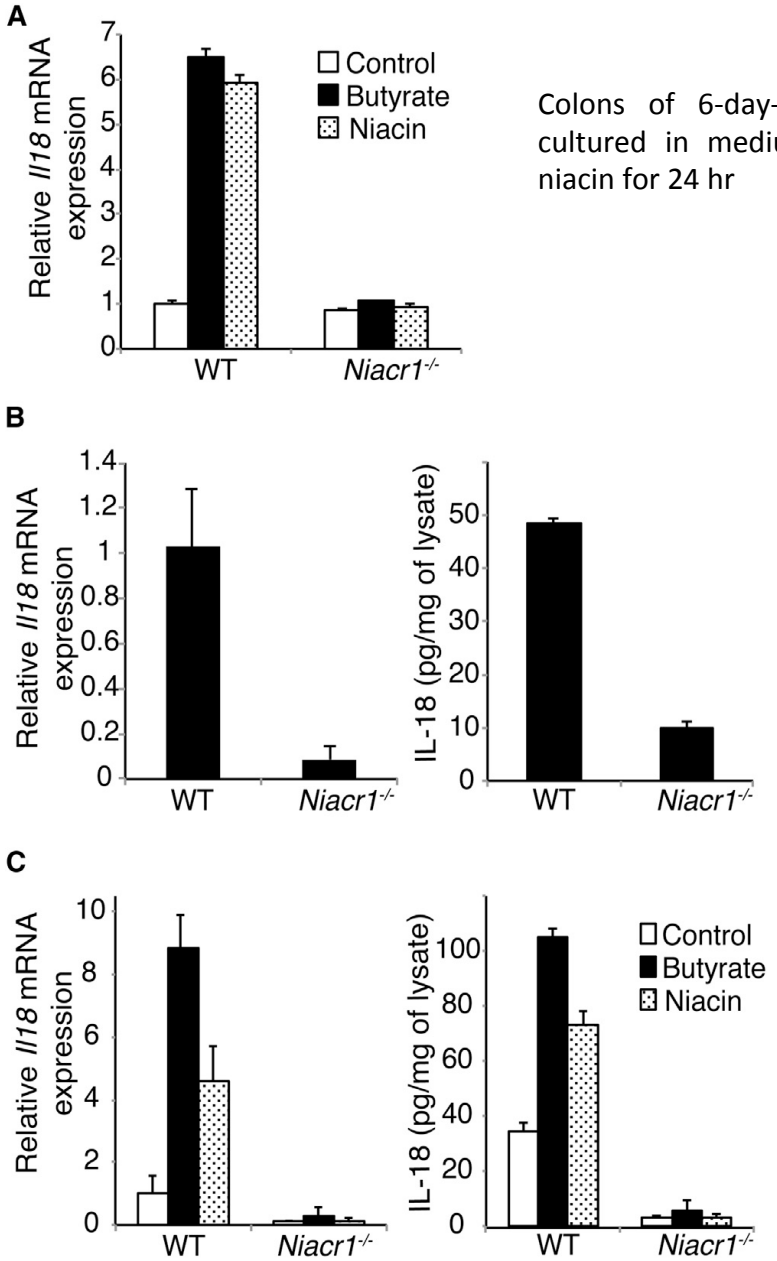
Fig.2 Naive OT-II CD4+CD25 T cells were differentiated with butyrate- or niacin-treated splenic DCs

Butyrate or Niacin Induce IL-18 Expression in Colonic Epithelium in a Gpr109a-Dependent Manner



Neonatal colon, in vitro stimulation 24h

Fig.S3



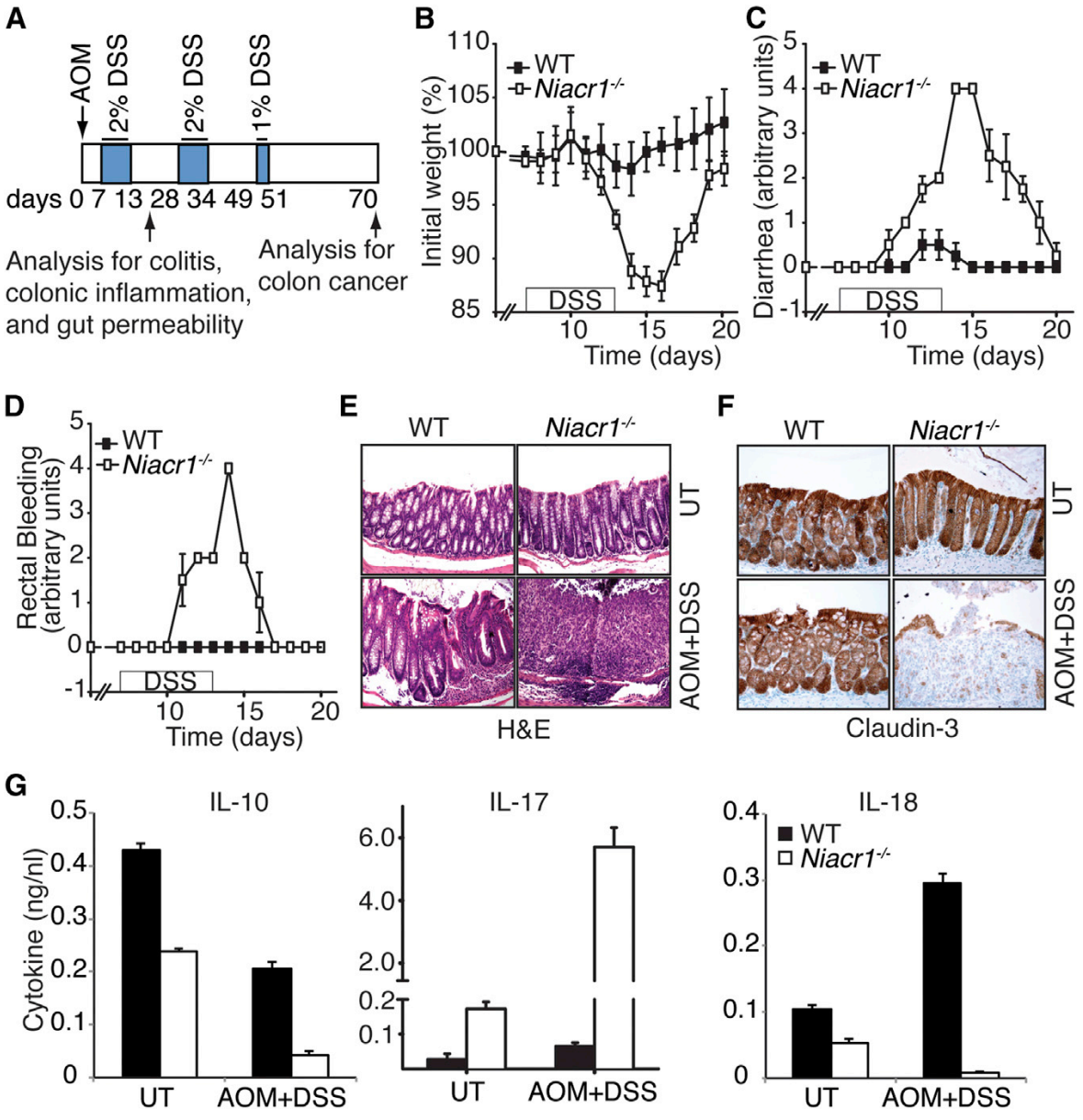
Colons of 6-day-old WT or Niacr1/ mice were cultured in medium with or without butyrate or niacin for 24 hr

colonic epithelial cells

One day after oral administration of butyrate or niacin in vivo, expression of IL-18 in colonic epithelium

Fig.3

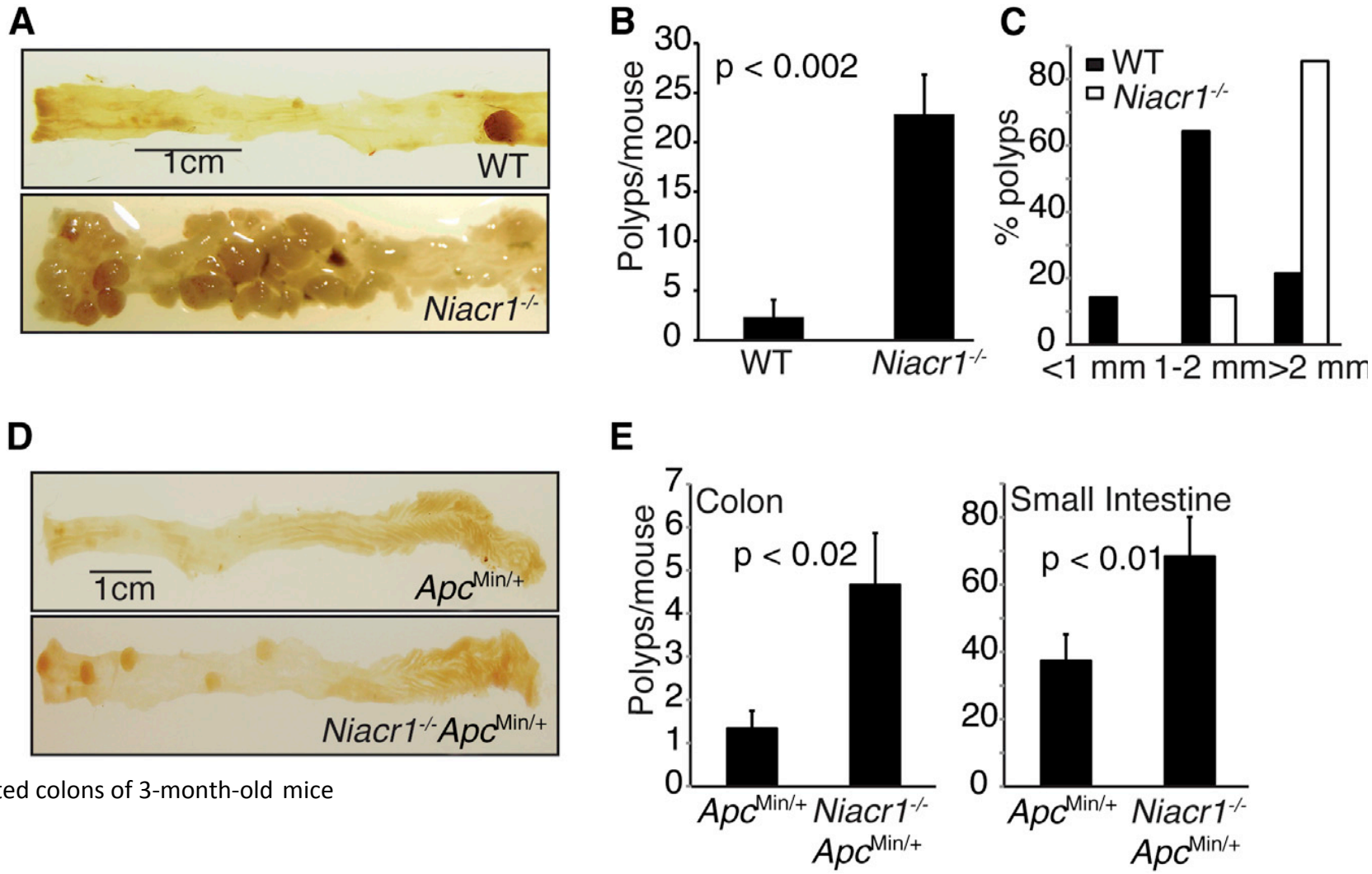
Gpr109a Deficiency Enhances Susceptibility to Lethal Colitis and Colonic Inflammation



in colons

Fig.4

GPR109a Deficiency Promotes Inflammation-Induced as well as $Apc^{Min/+}$-Driven Colon Carcinogenesis



dissected colons of 3-month-old mice

Fig.5

Gpr109a Expressed in Immune Cells as well as in Colonic Tissue Is Necessary for Protection against Colitis and Colon Carcinogenesis

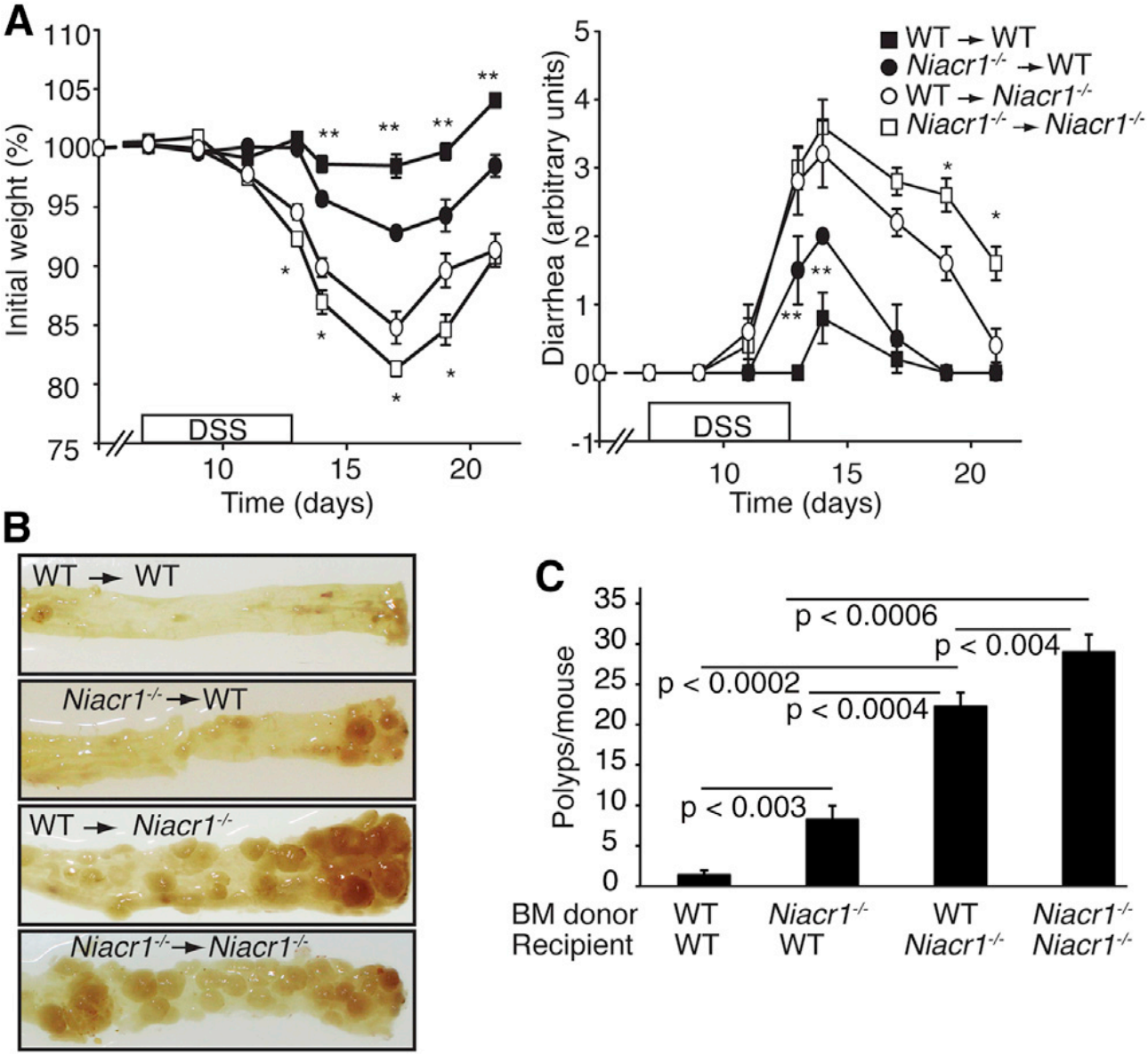


Fig.6

Activation of Gpr109a Suppresses Colonic Inflammation and Carcinogenesis in the Absence of Gut Microbiota

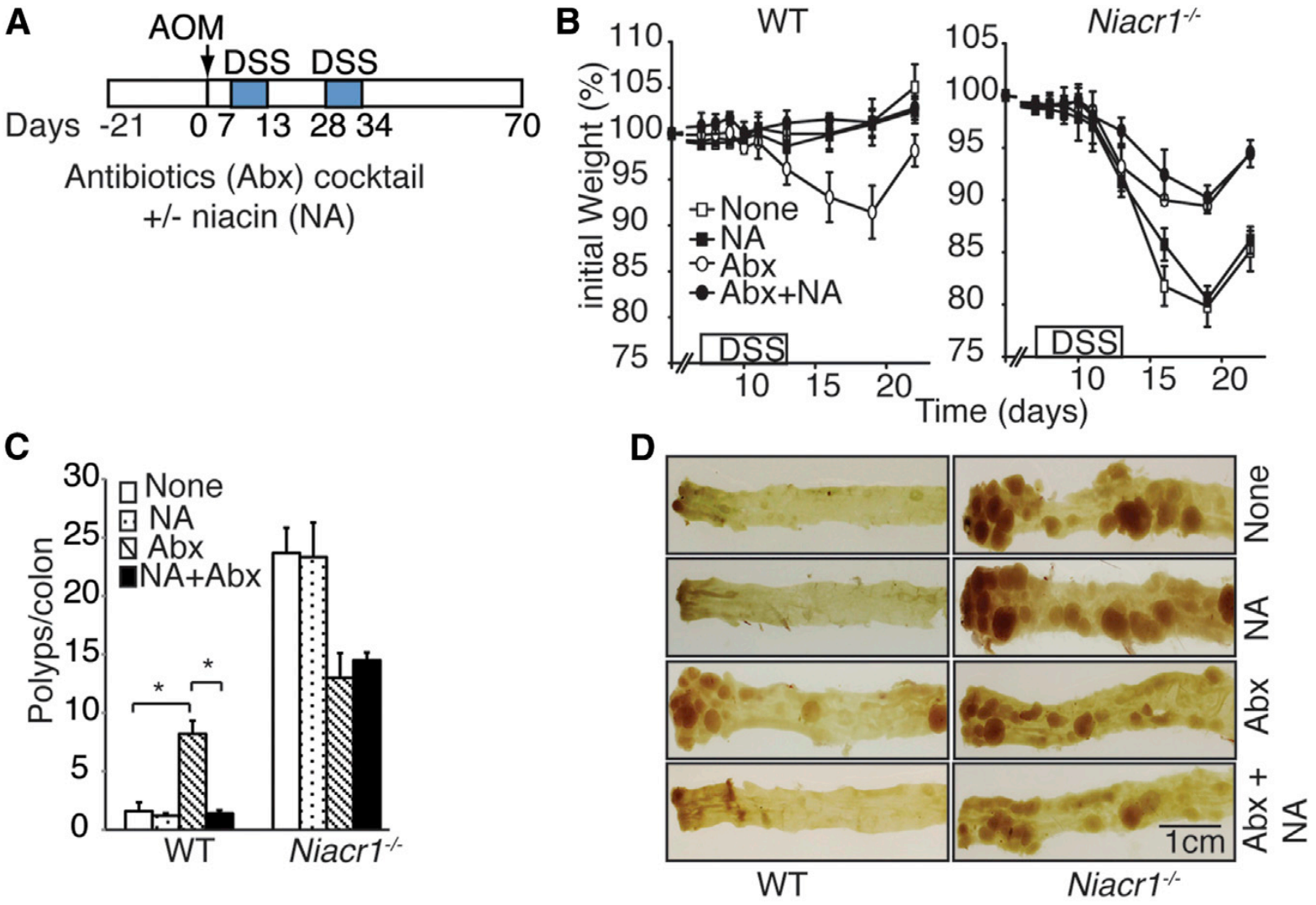


Fig.7

GPR109a Signaling plays an important role in suppressing the overgrowth of colitigenic bacteria

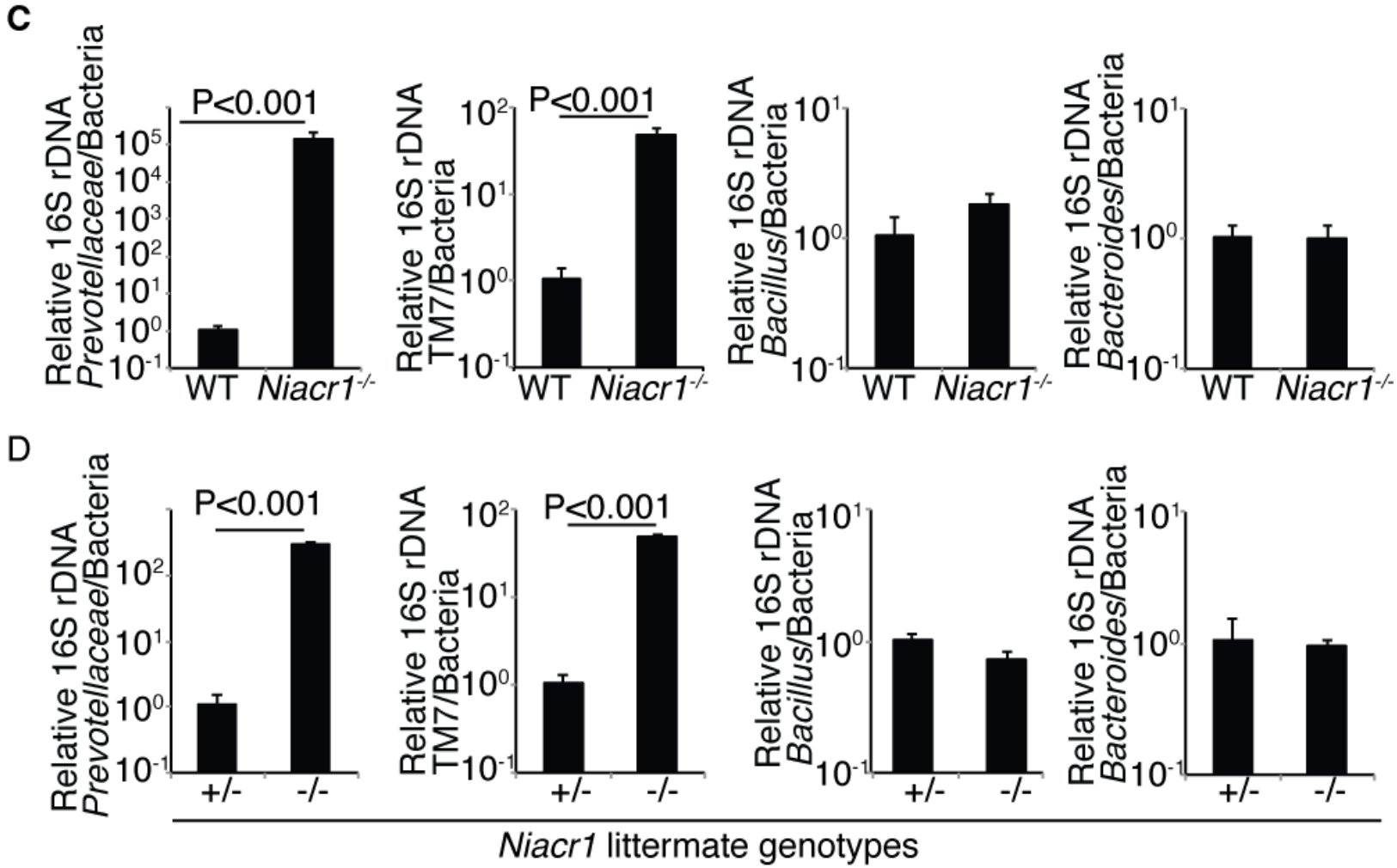


Fig.S6

Activation of Gpr109a Suppresses Colonic Inflammation and Carcinogenesis in the Absence of Dietary Fiber

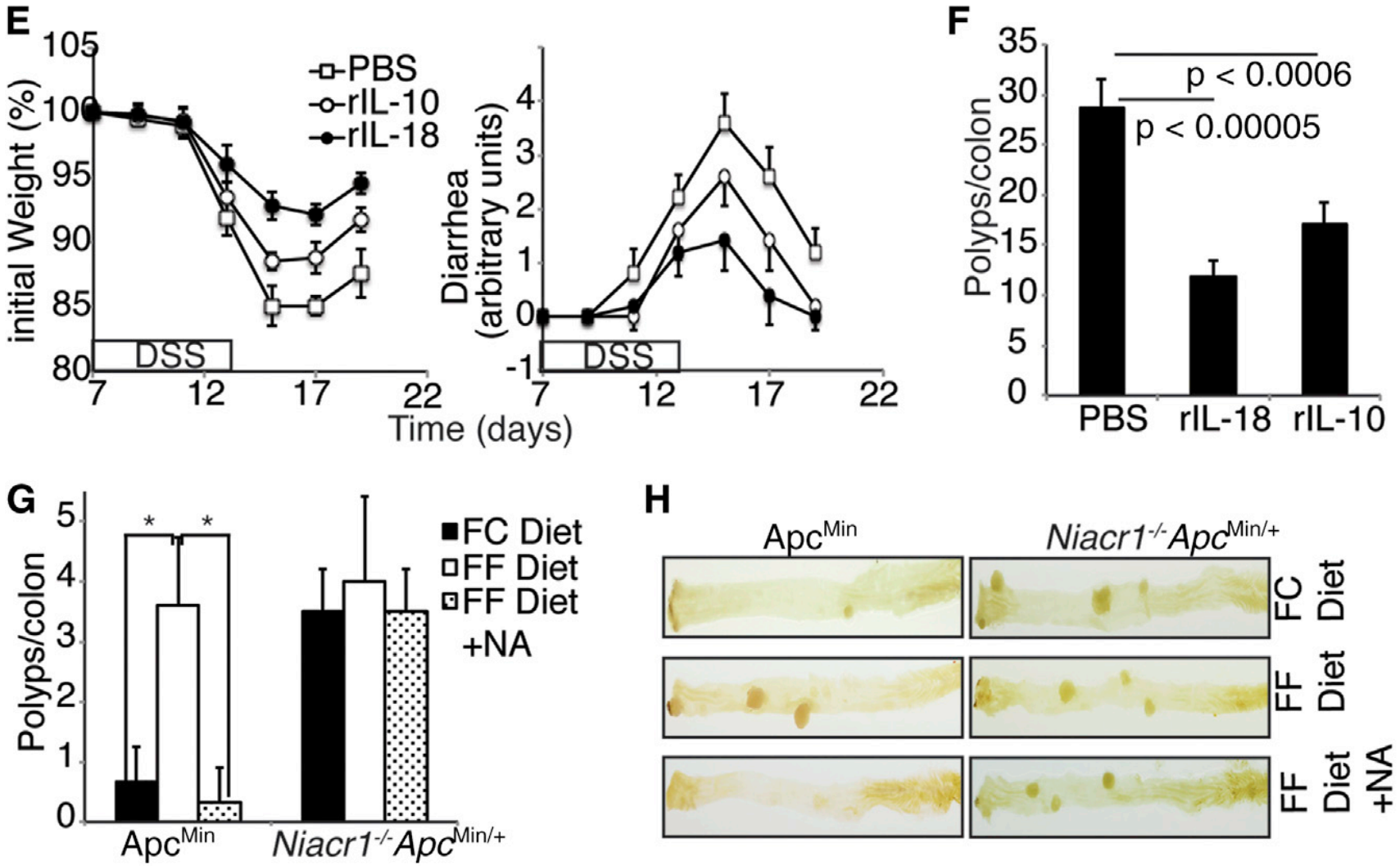
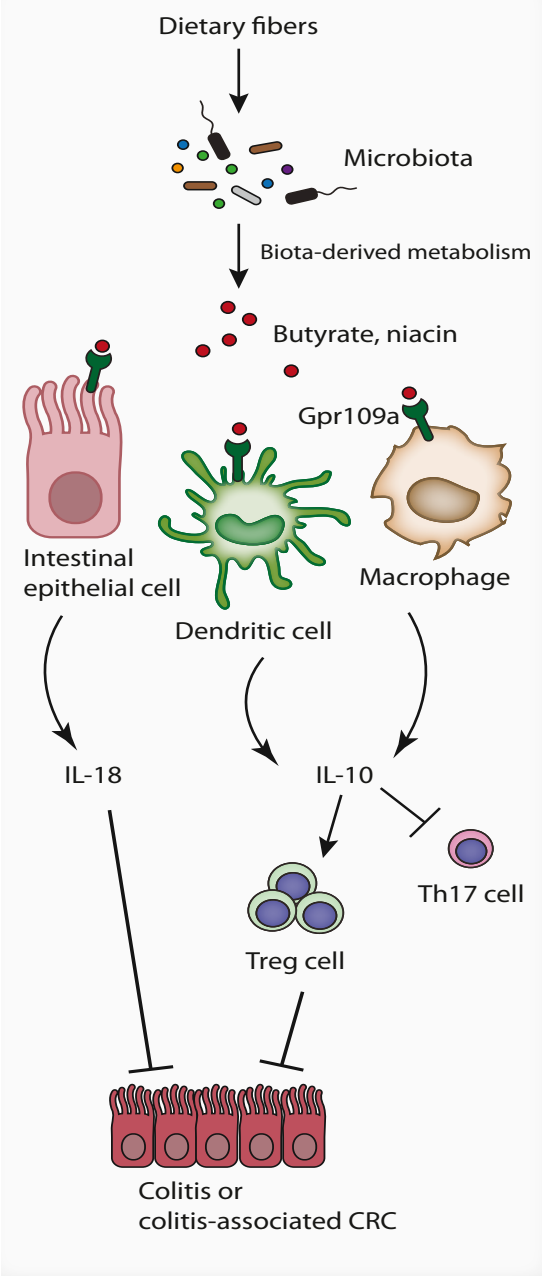


Fig.7

Conclusion



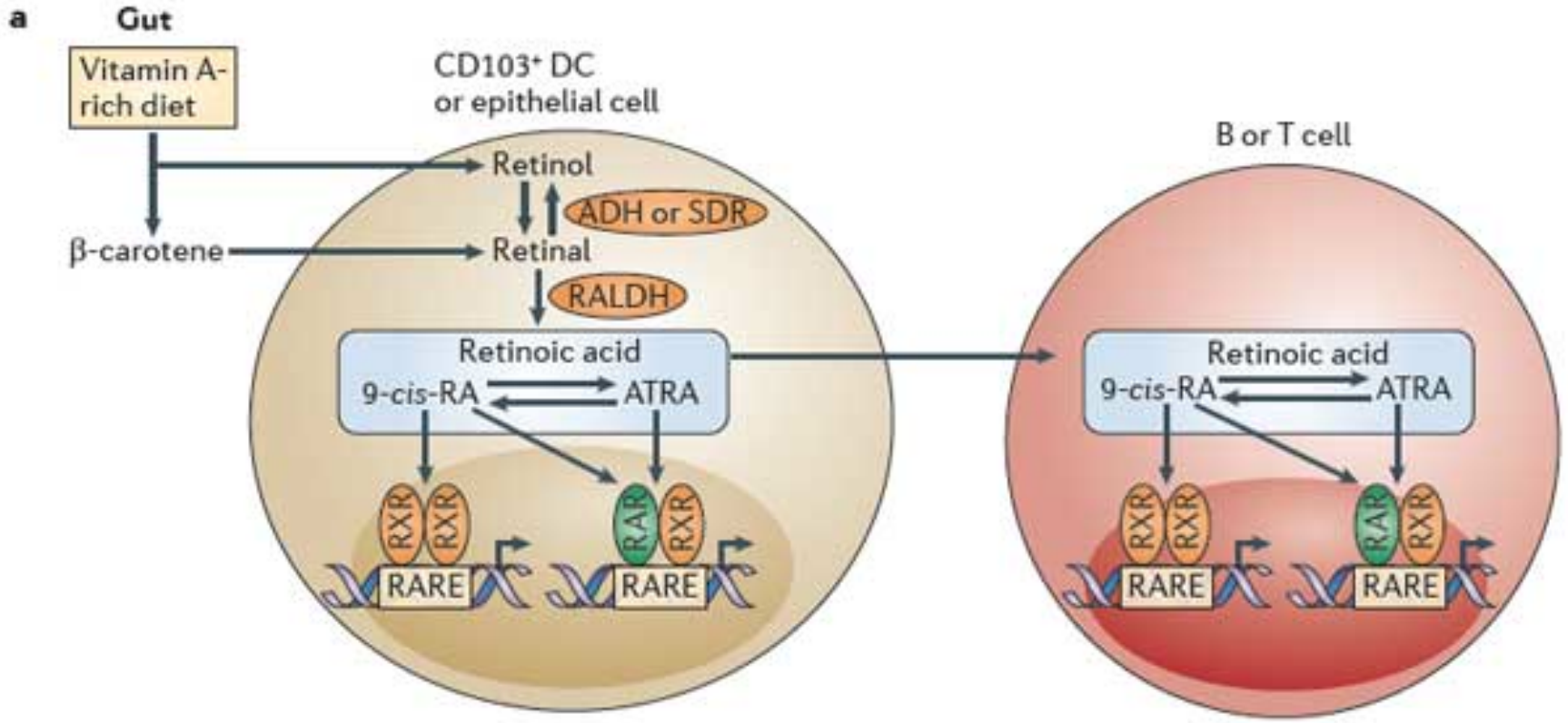
C. Jobin, Immunity 2014

Unique lamina propria stromal cells imprint the functional phenotype of mucosal dendritic cells

I Vicente-Suarez[1], A Larange[1], C Reardon[1], M Matho[2], S Feau[1], G Chodaczek[1], Y Park[1,3], Y Obata[4,5], R Gold[1], Y Wang-Zhu[1], C Lena[1], DM Zajonc[2], SP Schoenberger[1], M Kronenberg[1] and H Cheroutre[1]

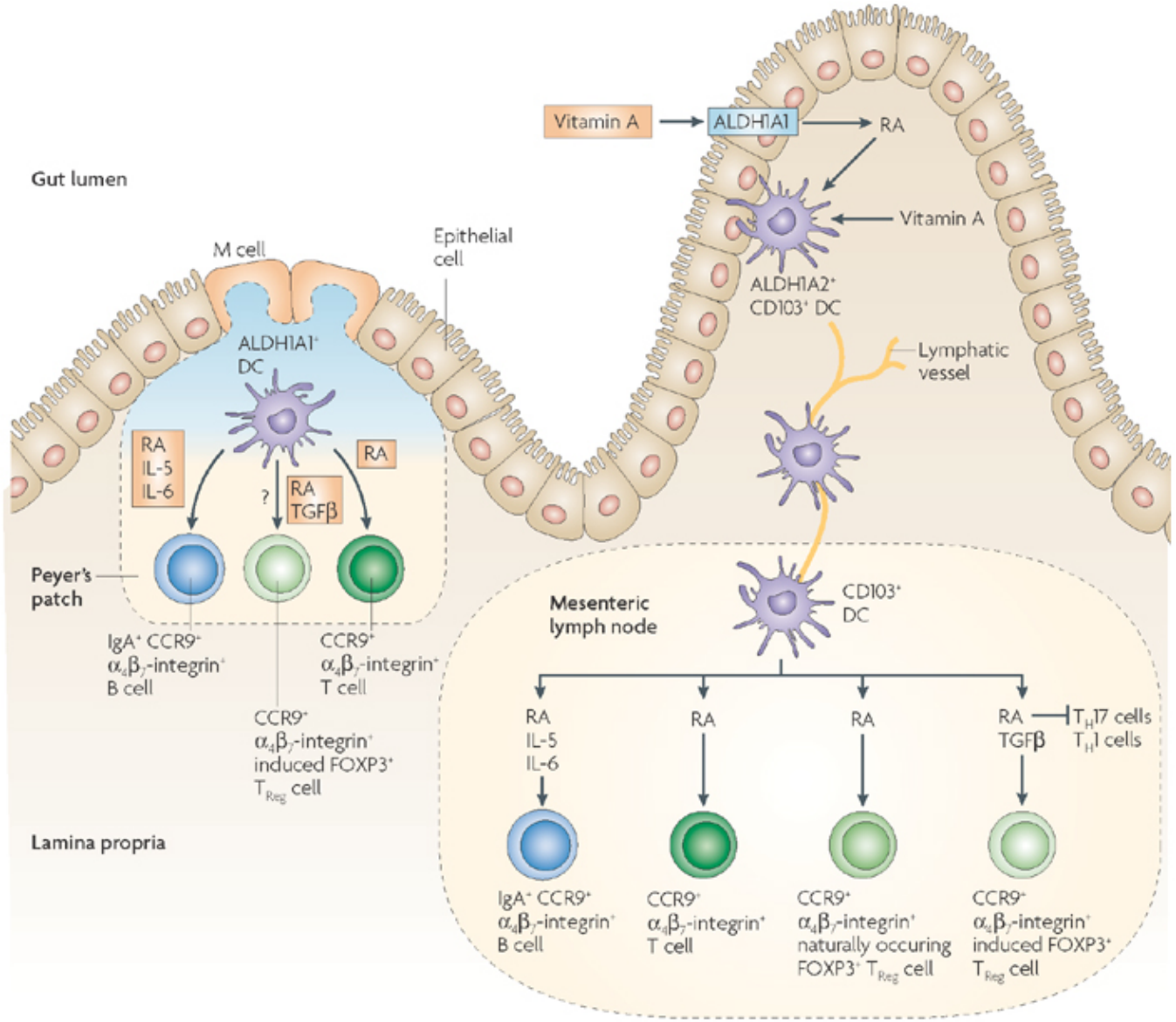
18 June 2014. doi:10.1038/mi.2014.51
MucosalImmunology

Background



Marc Veldhoen & Verena Brucklacher-Waldert, Nat Rev Immunol, 2012

Background

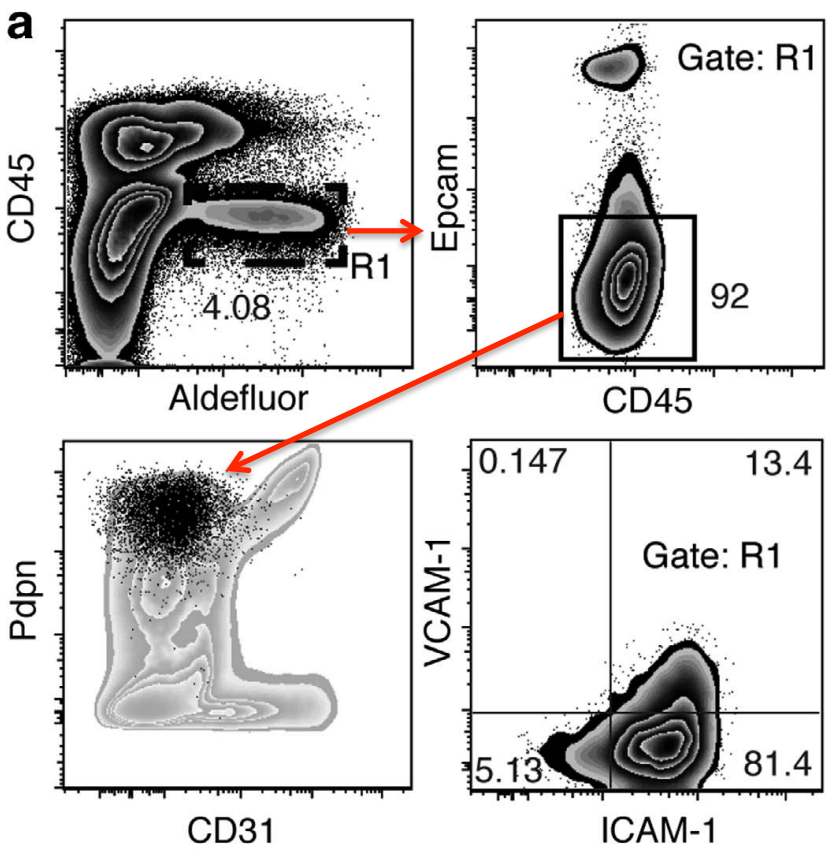


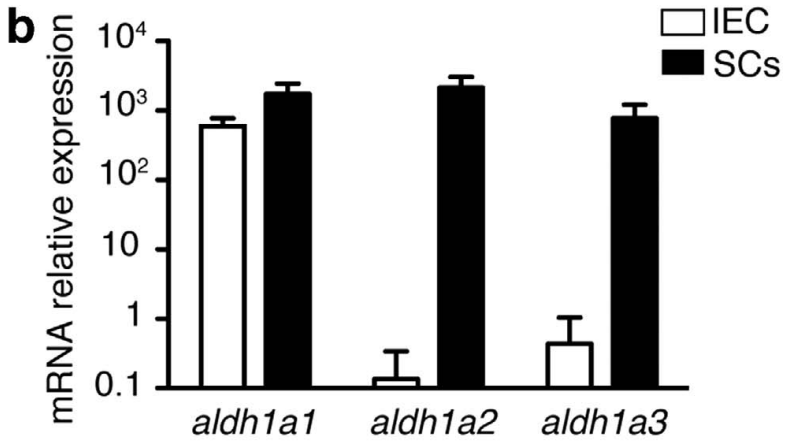
Janine L. Coombes & Fiona Powrie, Nat Rev Immunol 2008

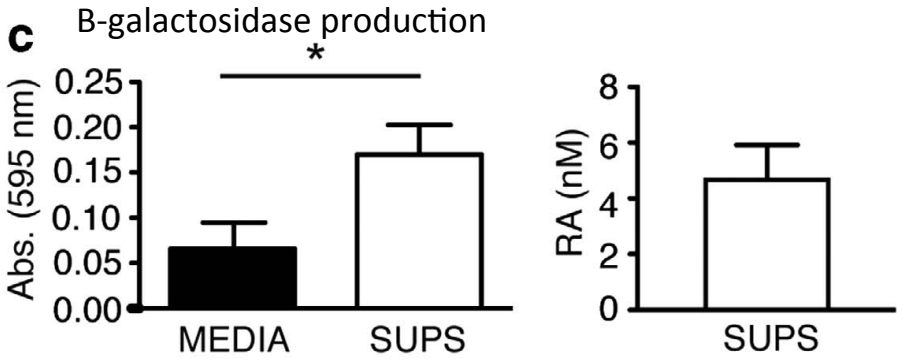
Nature Reviews | Immunology

A subset of lamina propria stromal cells have the capacity to produce retinoic acid

aldefluor, a fluorescent RALDH substrate that marks cells which have capacity to produce RA







supernatants from overnight cultures of aldefluor+ SCs were used to stimulate a reporter cell line that produces b-galactosidase under the control of a RARE.

Fig.1

Intestinal microbiota but NOT RA was required for the induction or maintenance of the RA metabolism machinery in LP SCs

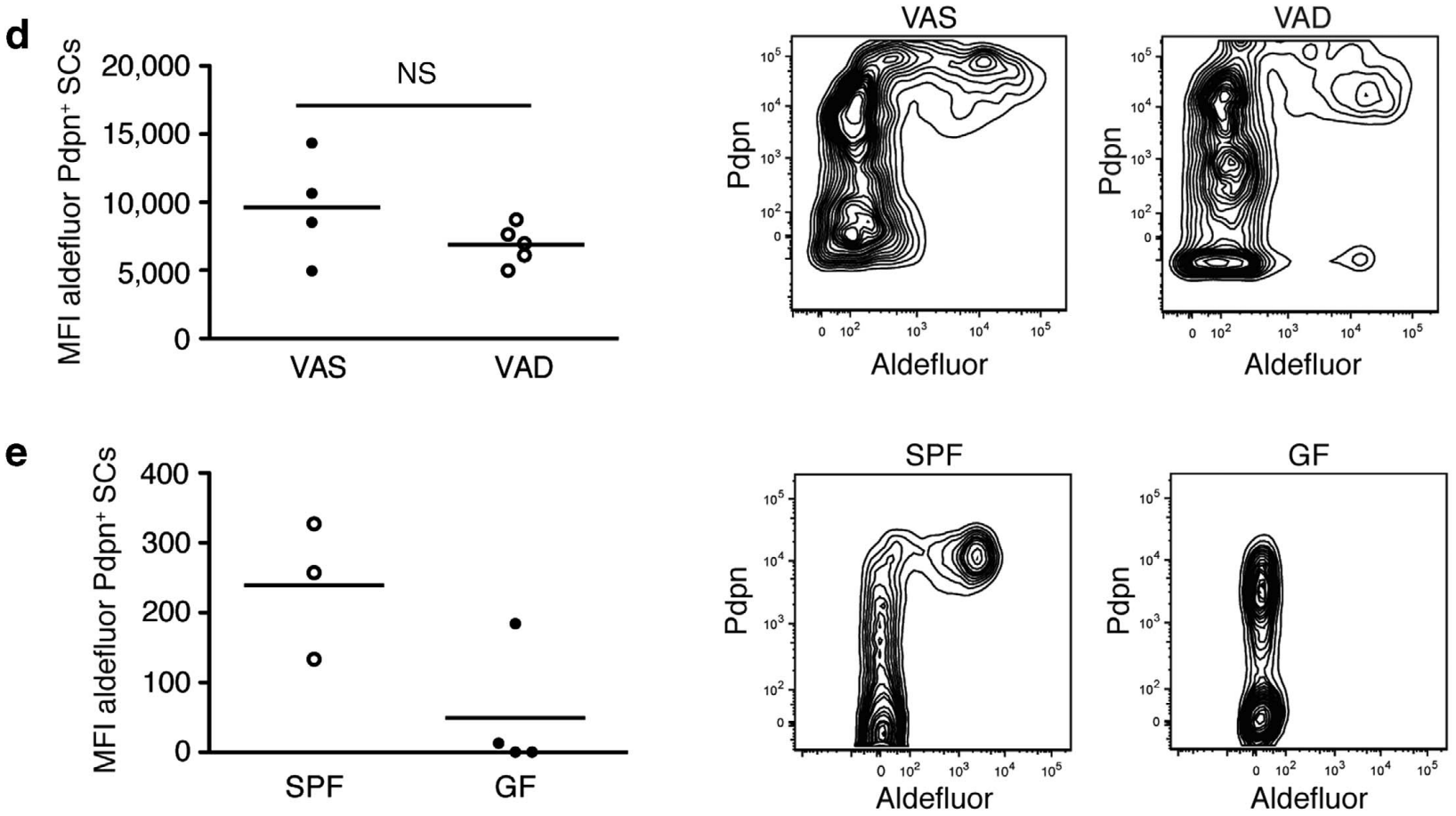


Fig.1

Aldefluor-positive stromal cells are abundant within the intestinal lamina propria and locate closely to intestinal dendritic cells.

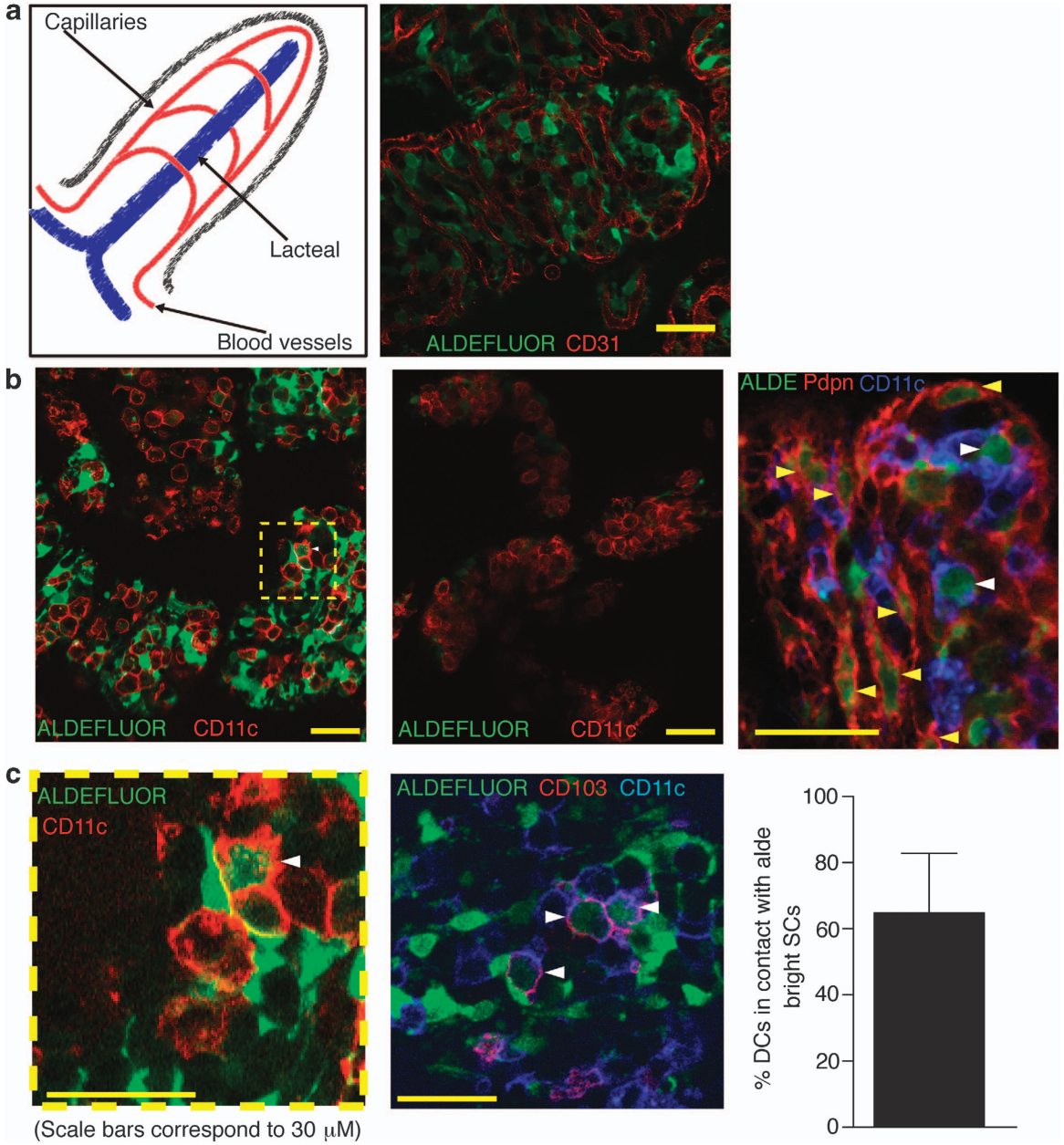
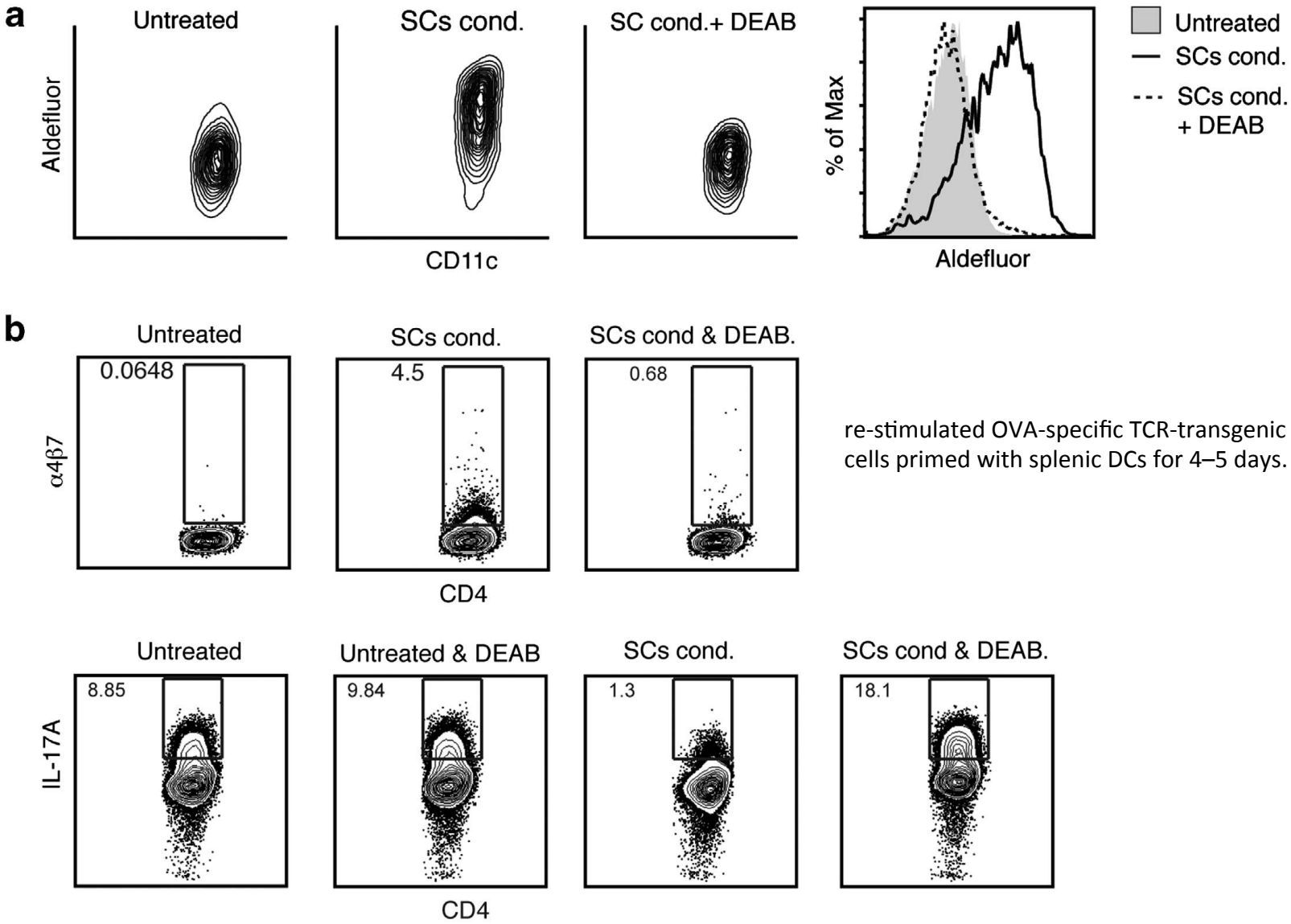


Fig.2

DCs require RAR signaling to induce RA-producing enzymes when cultured with Pdpn^{+} CD31^{-} SI LP SCs

Sorting of SI Pdpn+ CD31- SCs and cocultured for 24 h with splenic DCs.



re-stimulated OVA-specific TCR-transgenic CD4 T cells primed with splenic DCs for 4–5 days.

Fig.3

Dendritic cells require retinoic acid receptor signaling to induce RA-producing enzymes when cultured with Pdpn^{+} CD31^{+} SI LP SCs

Conditioning of splenic DCs for 24 h with media harvested from Pdp+CD31- SCs overnight cultures

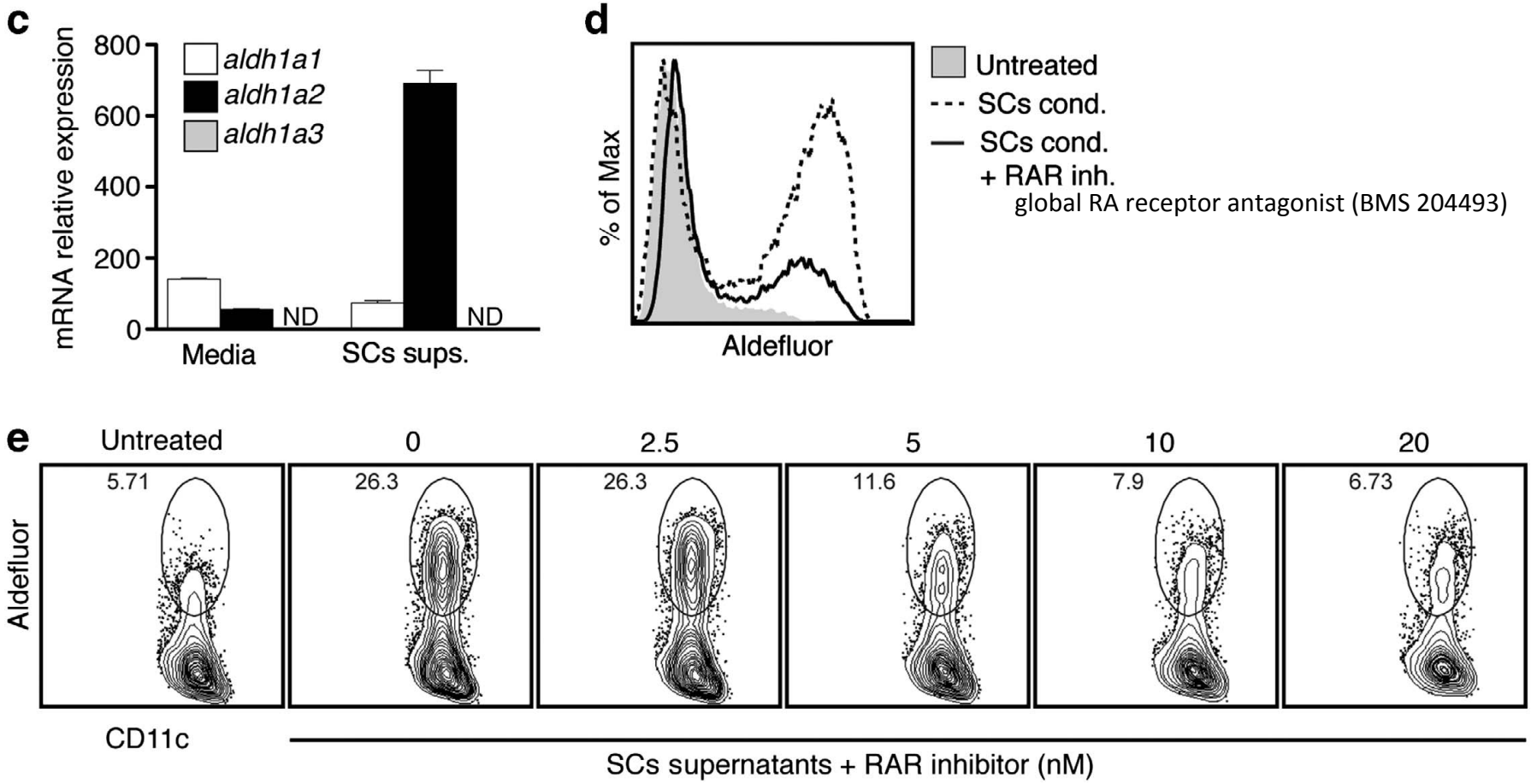


Fig.3

GM-CSF production by stromal cells is enhanced by dendritic cells and required for the imprinting of DCs with high RALDH activity.

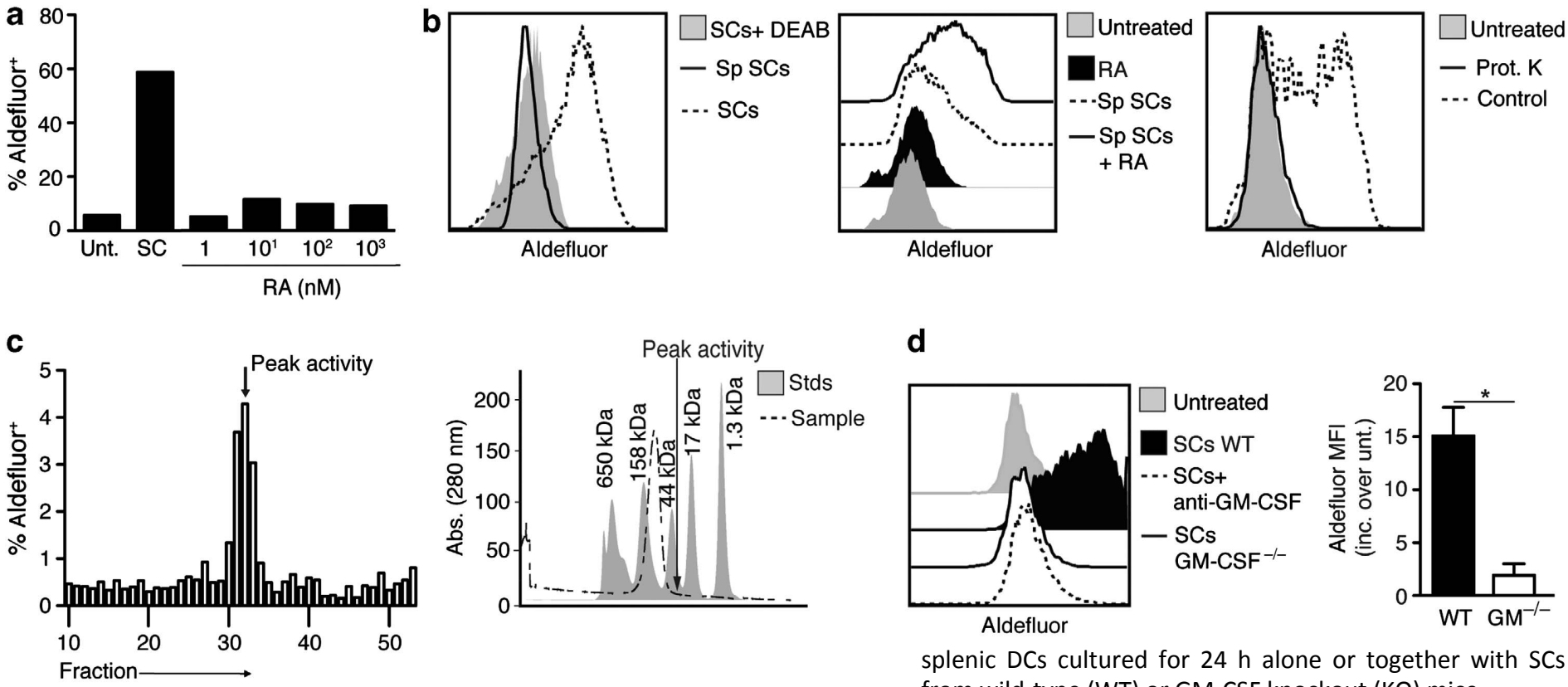
Fig.4

On splenic DCs after 24 h treatment

cell line established from sorted primary CD4- Pdpnhi splenic cells (Sp SCs) vs. SI LP CD45- Epcam- Pdpn+ CD31- stromal cells (SCs)

Splenic DCs cultured in different conditions.

splenic DCs treated with RA plus concentrated suspension (sups) from the aforementioned cell line.

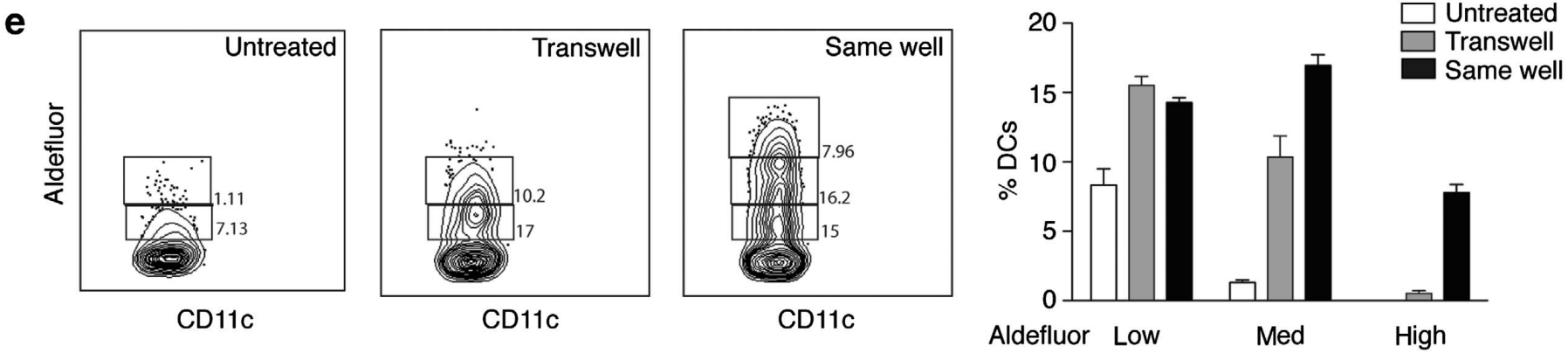


splenic DCs after 24 h treatment with RA plus sequential fractions of the sups from Sp SCs

splenic DCs cultured for 24 h alone or together with SCs from wild-type (WT) or GM-CSF knockout (KO) mice.

RA and GM-CSF produced by LP SCs synergize to imprint DCs with the ability to produce RA.

Splenic DCs after 24h culture with SI LP SCs in the same well or separated by a transwell



SI LP SCs cultured for 24 h alone or together with splenic DCs.

Fig.4

CD11b+ CD103+ DC numbers are diminished in GM-CSF-/- mice.

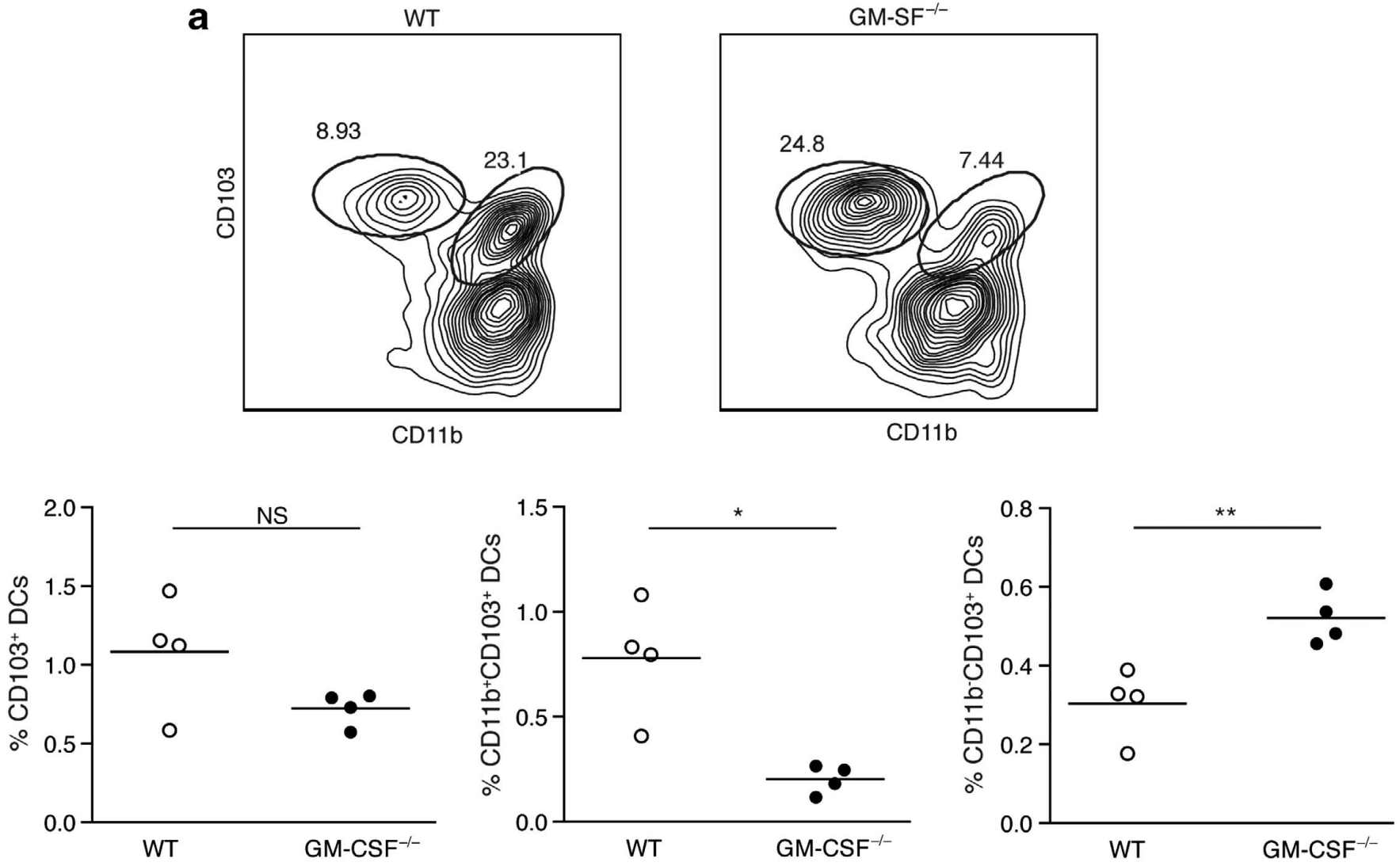


Fig.5

CD11b+ CD103+ DC RA-producing capacity is diminished in GM-CSF-/- mice.

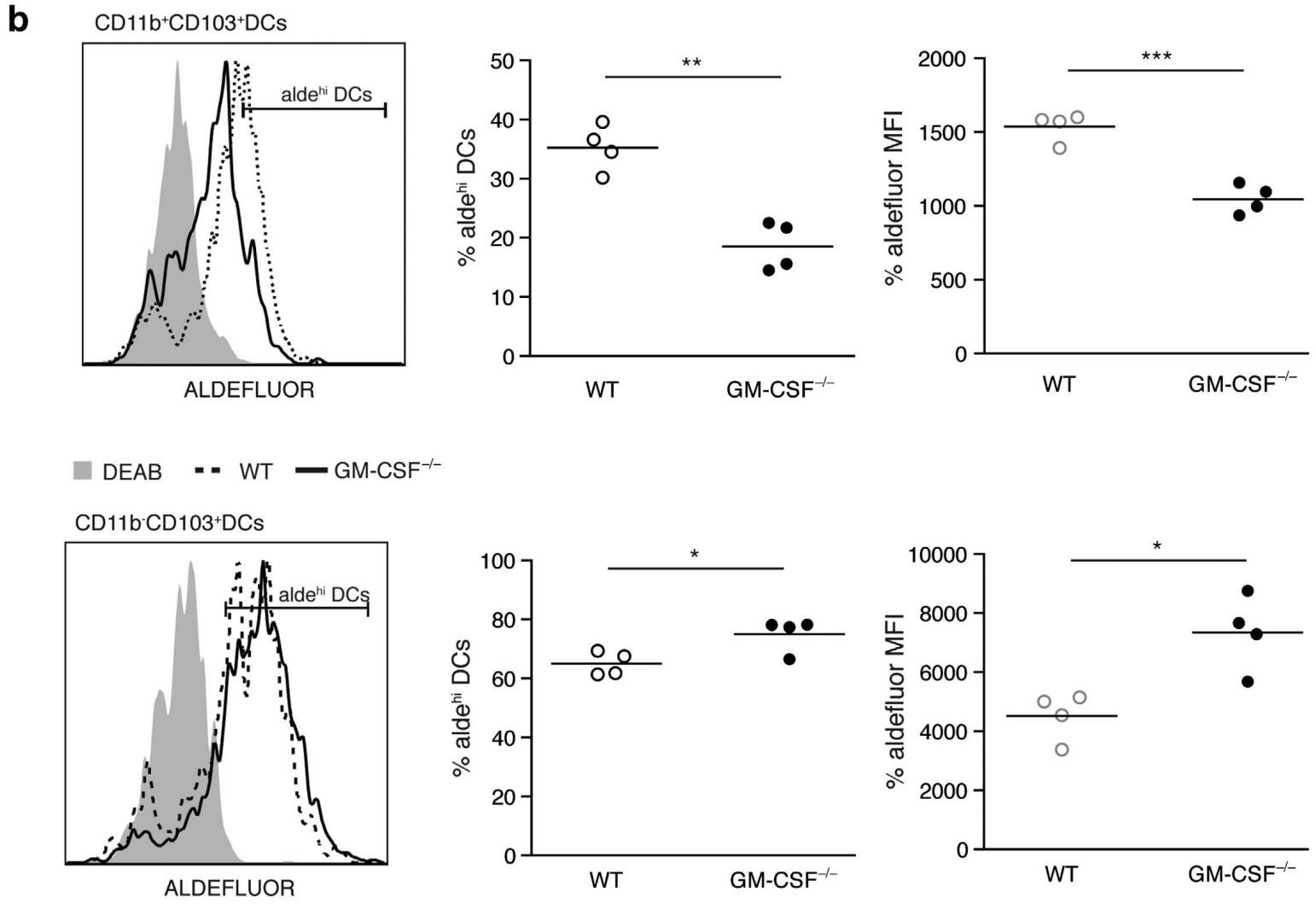


Fig.5

Conclusion

- A type of LP SCs as a new player in mucosal immune regulation, able to interact with local DCs and rendering them capable to produce RA.
- Intestinal LP SCs, unlike DCs, expressed RALDH enzymes constitutively and independently of Vitamin A.
- These SCs might serve as a primary source of RA for the initial education and imprinting of the RA-processing machinery in migratory DC precursor cells.
- Secreted RA alone is sufficient to induce RALDH2 expression in DCs, however additional factors and/or direct contact between DCs and SCs further promoted the functional education of the DCs.
- GM-CSF produced by LP SCs could be an important cofactor in this education.