4 (IRF4) (Fig. 4E), which endows T_{regs} with the ability to suppress T_H2 responses (*39*).

Type 2 responses are proposed to perform "housekeeping" repair functions co-opted for defense against large parasites (*40*). In germfree mice, type 2 immunity is exacerbated (*3*–*6*), possibly as a consequence of deregulated repair responses. In accordance with this view, expression of the type 2 cytokine IL-33 by epithelial cells is increased in germfree mice (Fig. 4F and fig. S11C). IL-33 promotes the accumulation and function of microbiota-independent (fig. S3) Gata3$^+$ T_{regs}, which express high levels of amphiregulin, an epidermal growth factor receptor ligand involved in tissue repair (*20*). In contrast, the microbiota induces type 3 responses through cytokines such as IL-6 and IL-23 (Fig. 4F) and thereby suppresses the default type 2 responses (Fig. 3 and fig. S13).

A model of the immune system may therefore be proposed in which type 1, 2, and 3 responses, induced by intracellular threats, tissue injury, and extracellular threats, respectively, establish a healthy equilibrium. In that model, T_{reg} subsets are part of each type of responses and play an essential role in balancing the number of effectors that are generated during steady state, infection, or injury. As we have evolved and developed in the presence of microbes, an absence of microbes leads to a loss in type 1 (*41*) and type 3 responses and, therefore, to deregulated type 2 responses associated with profibrotic and proallergic pathologies (*42*). A similar mechanism may account for the increase, in industrialized nations, of autoimmune pathologies associated with type 3 immunity (*1*).

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S13
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MUCOSAL IMMUNOLOGY

Individual intestinal symbionts induce a distinct population of RORγ$^+$ regulatory T cells

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T regulatory cells that express the transcription factor Foxp3 (Foxp3$^+$ T_{regs}) promote tissue homeostasis in several settings. We now report that symbiotic members of the human gut microbiota induce a distinct T_{reg} population in the mouse colon, which constrains immunoinflammatory responses. This induction—which we find to map to a broad, but specific, array of individual bacterial species—requires the transcription factor Rorγ, paradoxically, in that Rorγ is thought to antagonize FoxP3 and to promote T helper 17 (T_H17) cell differentiation. Rorγ's transcriptional footprint differs in colonic T_{regs} and T_H17 cells and controls important effector molecules. Rorγ, and the T_{regs} that express it, contribute substantially to regulating colonic T_H1/T_H17 inflammation. Thus, the marked context-specificity of Rorγ results in very different outcomes even in closely related cell types.

FoxP3 regulatory T (Foxp3$^+$ T_{reg}) cells are essential regulators of immunologic homeostasis and responses (*1*). Beyond their well-described role in regulating the activity of other immunocytes, T_{regs} located in parenchymal tissues control other, nonimmunological, processes. These "tissue T_{regs}" include those that reside in visceral adipose tissue and regulate metabolic parameters (*2*, *3*) and those that help channel inflammatory and regenerative events in injured muscle (*4*). The activities, transcriptomes, and T cell receptor (TCR) repertoires of these tissue T_{regs} are distinct from their counterparts in secondary lymphoid organs.

Another essential and specific population of tissue T_{regs} resides in the lamina propria (LP) of the digestive tract, in particular in the colon, where these cells modulate responses to commensal microbes [reviewed in (*5*)]. Colonic T_{regs} are an unusual population that has provoked some contradictory observations. TCRs expressed by colonic T_{regs} show marked reactivity against microbial antigens that seem to be important drivers of their differentiation and/or expansion (*6*, *7*). Many of them appear to arise by conversion from FoxP3$^-$ conventional CD4$^+$ T cells (T_{conv}) (*6*, *7*), although arguments for a

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thymic origin have been made (*7*). Many colonic T_{regs} express marker profiles (Helios$^-$ and Nrp1$^-$) that differ from T_{regs} of thymic origin [reviewed in (*8*)], although the importance of these markers has been questioned (*5*, *8*). Accordingly, most studies have found a decreased abundance of colonic T_{regs} in germ-free (GF) mice [reviewed in (*5*)], and colonization of GF mice by pools of microbes [Schadler's flora (*9*) or *Clostridia* combinations (*10*, *11*)] elicited the differentiation or expansion of Helios$^-$Nrp1$^-$ colonic T_{regs}. The ability of single microbes to induce colonic T_{regs} has been more controversial, and the need for complex combinations (*10*, *11*) has been questioned (*12*).

The transcriptomes of tissue-resident T_{regs} adapt to their location, most strikingly in terms of transcription factors (TFs) (*13*), and we searched for such elements in colonic T_{regs}. Comparison of transcriptomes of highly purified CD4$^+$FoxP3$^+$ T_{regs} [from *Foxp3*$^{ires-gfp}$ reporter mice (*14*)] from colon or spleen uncovered 933 differential transcripts [at a fold change >2 and false discovery rate (FDR) <0.1] [Fig. 1A (top), fig. S1A, and table S1]. These encompassed important signaling and effector pathways (*Icos*, *Gzmb*, *Lag3*, *Areg*, and *Il1rl1*) [Fig. 1A (top) and table S1], shared in a patchwork manner by other tissue T_{regs}. Yet ~39% (at a colon-specific bias of >1.5-fold) had preferential expression in colonic T_{regs} (including *Il10*, *Ctla4*, *Havcr2*, *Ccl20*, *Jak2*, and *Fosl2*) [Fig. 1A (bottom) and table S2]. GeneOntology analysis revealed no enriched function or pathway, except for a high proportion of TFs, including *Ahr*, *Epas1*,

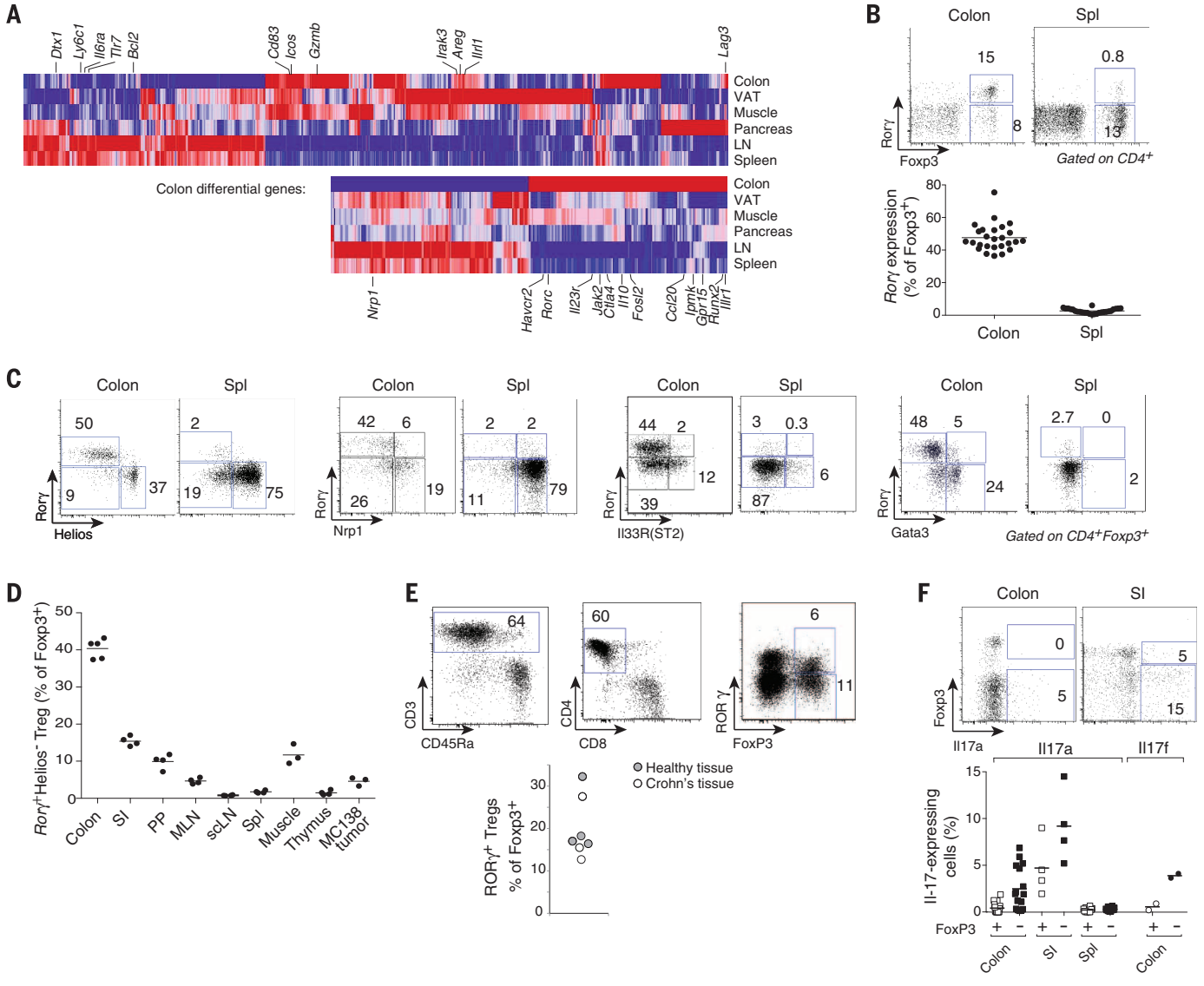


Fig. 1. Rorγ, encoded by *Rorc*, is preferentially expressed in colonic T_{regs}. Gene expression profiles from purified T_{reg} cells of various origins. (**A**) Transcripts that are enriched in tissue and colonic T_{regs}. (Top) Transcripts differentially represented in tissue versus splenic T_{regs} (at a fold change >2). VAT, visceral adipose tissue. (Bottom) Transcripts that are most biased in colonic T_{regs} (fold change >1.5 versus any other tissue T_{reg}). Means of at least two duplicates. (**B**) Representative flow cytometry plots of CD4$^+$ T cells and a compilation of frequencies (bottom) of Rorγ$^+$Helios$^-$ T_{regs} within the FoxP3$^+$CD4$^+$TCRβ$^+$ population. Each point is an individual mouse. Data are representative of more than three independent experiments. (**C**) Representative Rorγ versus Helios, Nrp1, IL-33R, or Gata3 plots for colon or spleen Foxp3$^+$CD4$^+$TCRβ$^+$ T_{regs} (see fig. S2 for quantification). (**D**) Frequencies of Rorγ$^+$Helios$^-$ T_{regs} among FoxP3$^+$CD4$^+$TCRβ$^+$ cells of different tissues (SI, small intestinal lamina propria; PP, Peyer's patches; MLN, mesenteric LNs; scLN, subcutaneous LNs; spleen, Spl). Each point is an individual mouse. Data pooled from at least two independent experiments. (**E**) Flow cytometry analysis of human colon biopsies and frequencies of human RORγ$^+$ T_{regs} within the FOXP3$^+$CD4$^+$CD8$^-$CD3$^+$CD45$^+$ population. Healthy tissue samples were endoscopically determined normal areas from chronic constipation or irritable bowel syndrome patients; inflamed tissue was from Crohn's lesions. Each point is an individual patient. Data pooled from five independent experiments. (**F**) IL-17a (after phorbol 12-myristate 13-acetate + ionomycin activation and intracellular staining) or IL-17f (reporter in *Il17f*^{rfp} mice) expression among Foxp3$^+$ T_{reg} or FoxP3$^-$ T_{conv} mice. Each point is an individual mouse. Data are representative of three independent experiments.

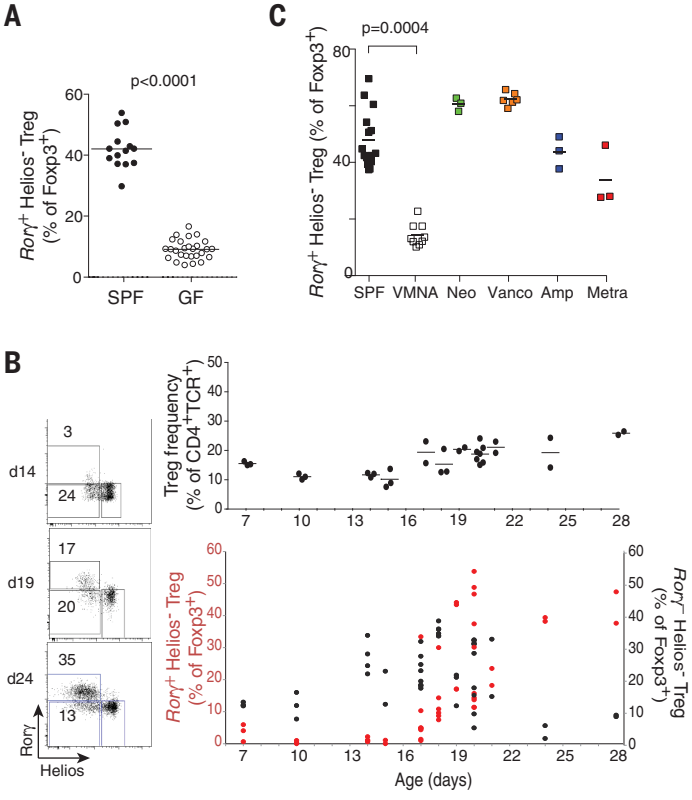
Hey1, *Bcl6*, *Npas2*, *Nr1d1*, and *Maf*. To our surprise, the most differential of these TFs proved to be *Rorc* (encodes Rorγ) (fig. S1B). Rorγ controls many aspects of immunocyte differentiation (*15*) but is perhaps best known as the key regulator of interleukin-17 (IL-17)–producing CD4$^+$ T cells (T_H17), and as a reciprocal antagonist of FoxP3 during in vitro differentiation in which CD4$^+$FoxP3$^+$ T_{reg} and T_H17 represent alternative cell fates [reviewed in (*16*)].

Cytometry confirmed that many colonic CD4$^+$FoxP3$^+$ T_{regs} express Rorγ (40 to 60% in C57BL/6J or other inbred mouse strains) (Fig. 1B and fig. S2A), a phenotype largely absent in spleen or lymph node (LN) and among FoxP3$^+$ cells induced in vitro. Helios and Nrp1, described as markers of thymus-derived T_{regs} [reviewed in (*8*)], were absent on colonic Rorγ$^+$ T_{regs} (Fig. 1C); this absence demarcated three distinct subsets of colonic T_{regs}, with Rorγ$^+$ representing the majority of Helios$^-$ cells (Fig. 1C and fig. S2, B and C). Consistent with the RNA data, Rorγ$^+$ T_{regs} were also detected in low proportions in the small intestine (SI) and regenerating muscle (Fig. 1D and fig. S2D). In keeping with a recent report (*17*), Rorγ$^+$ T_{regs} were distinct from those expressing the IL-33 receptor, most of which were Helios$^+$ (Fig. 1D and fig. S2, B, C, E, and F), and from Gata3^{hi} T_{regs} (*18*), which also belong to the Helios$^+$ T_{reg} subset (Fig. 1D and fig. S2, B and C).

We asked whether RORγ is also expressed by colonic T_{regs} in humans, by staining cells from healthy or inflamed (Crohn's) colon biopsies. Rorγ$^+$ T_{regs} were indeed detected at comparable levels in both contexts (Fig. 1E).

Rare T_{regs} expressing IL-17 and Rorγ have been observed during chronic inflammation or cancer, usually being Helios^{hi} [reviewed in (*19*)]. We tested IL-17 production in colonic Rorγ$^+$ T_{regs}. Although IL-17–expressing T_{regs} could be detected in the SI LP, colonic Rorγ$^+$ T_{regs} did not secrete detectable IL-17a or f (Fig. 1F).

The properties of this dominant colonic Rorγ$^+$Helios$^-$ T_{reg} population suggested a link to the gut microbiota. Indeed, GF mice had a lower proportion of Rorγ$^+$ T_{regs} than their conventionally raised specific pathogen–free (SPF) counterparts (Fig. 2A). During normal maturation in the mouse, Rorγ$^+$ T_{regs} appeared between 15 and 25 days of age (Fig. 2B), coincident with the changes in the gut microbiota that accompany the transition to solid food. Note that Rorγ$^+$ T_{regs} appeared a few days after Rorγ$^-$Helios$^-$ T_{regs}. Antibiotic treatment strongly affected Rorγ$^+$ T_{regs} (Fig. 2C), a large reduction followed a broad-spectrum antibiotic combination, whereas individual antibiotics had less or no effect, which suggested the contribution of several microbes. As the reported impacts of various microbial species on total colonic T_{regs} have differed (*10*, *12*), we took advantage of a panel of mice generated in a large-scale screen in which GF mice were colonized with a single species from a panel of 22 bacterial species from the human gastrointestinal tract (table S3). A number of microbes elicited colonic Rorγ$^+$ T_{regs}, with a gradient of responses and, for some, at frequencies comparable with those of SPF mice (Fig. 2D). This restoration of Rorγ$^+$ T_{regs} was independent of bacterial load and not accompanied by inflammation (fig. S3). Bacteria able to induce Rorγ$^+$ T_{reg} (and colonic FoxP3$^+$ T_{regs} more generally) belonged to several phyla and genera and were not restricted to *Clostridiae* (*10*, *11*). Segmented filamentous bacteria (SFB)—which are classic inducers of Rorγ-dependent T_H17 cells (*20*) and which elicit IL-17–producing T_{regs} in the SI (*21*)—were only mediocre inducers of colonic Rorγ$^+$ T_{regs}, which reinforced the distinction between the cell populations. We noticed diversity within the *Bacteroides* genus and assessed a wider *Bacteroides* panel (fig. S4A and table S3). Here again, a range of colonic Rorγ$^+$ T_{regs} was observed. This distribution did not relate to the *Bacteroides* phylogeny for these strains, and there was no unique correlation



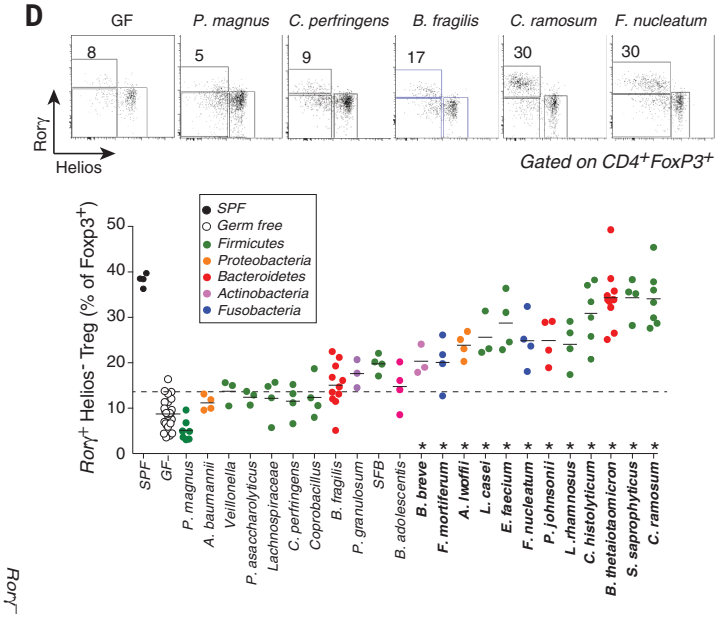


Fig. 2. Rorγ$^+$Helios$^-$ T_{regs} can be induced by several bacterial species. (**A**) Frequency of Rorγ$^+$Helios$^-$ within colon FoxP3$^+$CD4$^+$TCRβ$^+$ T_{regs} of SPF and GF mice, $P < 0.0001$ as determined by Student's t test. Each point is an individual mouse. Data pooled from more than three experiments. (**B**) Induction of Rorγ in colonic T_{regs} during postnatal development in SPF mice (left). Representative FACS plots (right); frequencies across ages of FoxP3$^+$ T_{regs} within CD4$^+$TCRβ$^+$ cells, as well as Rorγ$^+$Helios$^-$ (red) and Rorγ$^-$Helios$^-$ (black) cells within T_{regs}. Each point is an individual mouse. Data pooled from four or more experiments. (**C**) SPF mice were treated with single antibiotics (abbreviations for neomycin, vancomycin, ampicillin, metronidazole) or all four (VMNA) antibiotics for 4 weeks. Frequency of colonic Rorγ$^+$Helios$^-$ T_{regs} within the FoxP3$^+$CD4$^+$TCRβ$^+$ population. $P = 0.0004$, Bonferroni-corrected Student's t test. Each point is an individual mouse. Data pooled from two experiments. (**D**) GF mice were colonized with single bacterial species, and colonic T_{regs} were analyzed after 2 weeks (top). Representative plots and frequencies of Rorγ$^+$Helios$^-$ within FoxP3$^+$CD4$^+$TCRβ$^+$ T_{regs}, color-coded per phyla (bottom). Each point is an individual mouse. Data are representative one to three experiments for each microbe. *Different from GF at an FDR of <0.05.

between T_{reg}-inducing ability and gene content (fig. S4B). Colonic Rorγ$^+$ T_{regs} did not appear immediately after GF colonization but only after a few days, again after Rorγ$^-$Helios$^-$ cells (fig. S4C).

Several reports have suggested that short-chain fatty acids (SCFAs) promote increased colonic T_{regs} (*22*–*24*). To test their relevance to Rorγ$^+$ T_{regs}, SCFAs were quantified by liquid chromatography–mass spectrometry (LC-MS) in cecal content of monocolonized mice. No significant correlation was observed between any SCFA and Rorγ$^+$ T_{reg} frequency or to other T_{reg} parameters (fig. S5, A and B, and table S4). In addition, we could not reproduce previously reported effects of oral or rectal SCFA administration (fig. S5, C and D). Although SCFA combinatorial effects or intercolony variation cannot be ruled out, SCFAs cannot alone explain the microbial impact on colonic T_{regs} observed here.

To integrate our observations with intercellular pathways that influence intestinal T cells, we measured the relative abundance of Rorγ$^+$ T_{regs} in mice lacking receptors for key cytokines and alarmins. Signaling through IL-23, IL-1, or IL-33 receptors was not required to sustain Rorγ$^+$ T_{regs}, nor was IL-10 (fig. S6, A to D). In fact, only the Helios$^+$ population expanded after IL-33 administration (fig. S6E).

We then asked what transcripts Rorγ controls in Rorγ$^+$ T_{regs} and whether Rorγ is necessary to specify this particular T_{reg} lineage. We compared transcriptomes of Rorγ$^+$ and Rorγ$^-$ colonic T_{regs} (sorted from *Foxp3*$^{Thy1.1}$ × *Rorc*^{gfp} intercrossed mice). Rorγ$^+$ cells were enriched in some, but not all, transcripts of the colonic T_{reg} signature, notably *Il23r*, *Cxcr3*, *Tbx21*, and *Havcr2* (Fig. 3A), as validated at the protein level, including the unexpected CXCR3 (Fig. 3B). Conversely, *Il1rl1* (encodes IL-33R), *Nrp1*, and *Ikzf2* were underrepresented in Rorγ$^+$ T_{regs}.

To further delineate the transcriptional signature of Rorγ in T_{reg} cells, RNA sequencing profiles were generated from Nrp1$^-$ cells of *Foxp3-cre.Rorc*$^{fl/fl}$ mice, which have a T_{reg}-selective deletion of *Rorc* (fig. S7A), or paired wild-type (WT) littermates. Differentially expressed genes were related to the Rorγ-dependent signature in conventional T_H17 cells (defined from a comparison of SI CD4$^+$ T cells of mice colonized, or not, with SFB) (Fig. 3C and table S5). Part of the classic T_H17 signature was unrelated to Rorγ in colonic T_{regs} (blue in Fig. 3C) or *Il1r1* or the canonical T_H17 cytokines *Il17a/f* and *Il22*; some were shared (*Rorc* itself, *Il23r*); and a third segment was controlled by Rorγ in Nrp1$^-$ colonic T_{regs} but not in T_H17 cells (*Havrc2*, *Irak3*, and *Il1rn*). Thus, the transcriptional footprint of Rorγ is context-dependent in different T cells.

Next, we explored whether Rorγ contributes to colonic T_{reg} homeostasis. First, mice were treated for 3 weeks with a pharmacologic Rorγ antagonist (*25*), which reduces SI T_H17 levels. This treatment partially decreased both the total frequency of colonic FoxP3$^+$ cells and their Rorγ$^+$ component (Fig. 3D). Second, *Foxp3-cre.Rorc*$^{fl/fl}$ mice—which have no systemic T_{reg} deficiency or *scurfy*-like

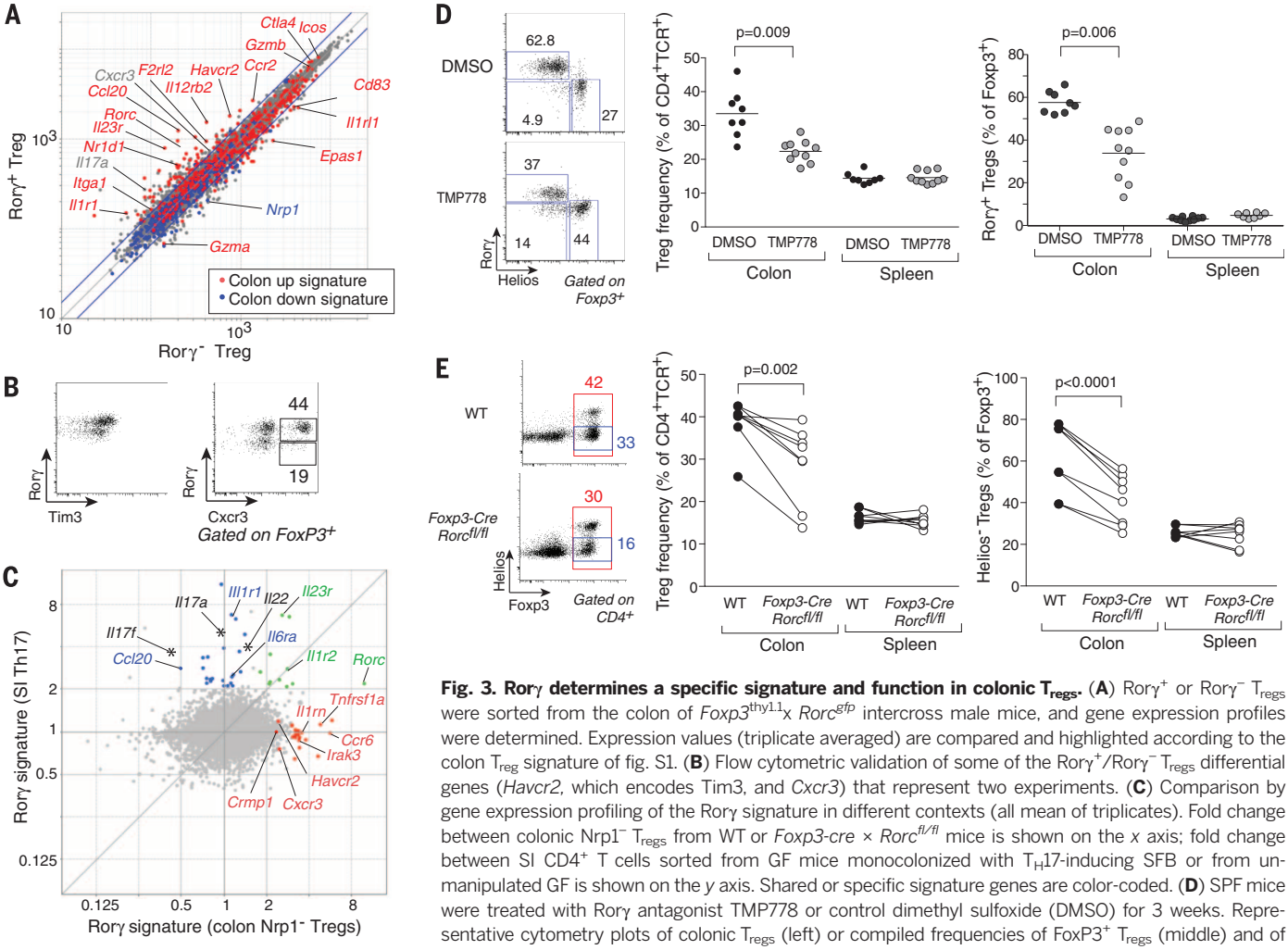


Fig. 3. Rorγ determines a specific signature and function in colonic T_{regs}. (**A**) Rorγ$^+$ or Rorγ$^-$ T_{regs} were sorted from the colon of *Foxp3*$^{thy1.1}$x *Rorc*^{gfp} intercross male mice, and gene expression profiles were determined. Expression values (triplicate averaged) are compared and highlighted according to the colon T_{reg} signature of fig. S1. (**B**) Flow cytometric validation of some of the Rorγ$^+$/Rorγ$^-$ T_{regs} differential genes (*Havcr2*, which encodes Tim3, and *Cxcr3*) that represent two experiments. (**C**) Comparison by gene expression profiling of the Rorγ signature in different contexts (all mean of triplicates). Fold change between colonic Nrp1$^-$ T_{regs} from WT or *Foxp3-cre* × *Rorc*$^{fl/fl}$ mice is shown on the *x* axis; fold change between SI CD4$^+$ T cells sorted from GF mice monocolonized with T_H17-inducing SFB or from unmanipulated GF is shown on the *y* axis. Shared or specific signature genes are color-coded. (**D**) SPF mice were treated with Rorγ antagonist TMP778 or control dimethyl sulfoxide (DMSO) for 3 weeks. Representative cytometry plots of colonic T_{regs} (left) or compiled frequencies of FoxP3$^+$ T_{regs} (middle) and of Rorγ$^+$Helios$^-$ (right) within FoxP3$^+$CD4$^+$TCRβ$^+$ T_{regs} (right); *P* = 0.009 as determined by Student's *t* test. Each point is an individual mouse. Data are representative of two or more independent experiments. (**E**) Analysis of Rorγ–deficient T_{regs} from *Foxp3-cre* × *Rorc*$^{fl/fl}$ mice or control (*Foxp3-creRorc*$^{+/+}$) littermates. Cytometry plots of colonic T_{regs} (left) or compiled frequencies of FoxP3$^+$ T_{regs} (middle) and of Rorγ$^+$Helios$^-$ (right) within FoxP3$^+$CD4$^+$TCRβ$^+$ T_{regs} (right); *P* values were determined by paired Student's *t* test. Each point is an individual mouse. Data are representative of more than three independent experiments.

pathology nor any change in FoxP3 intensity—showed a reduced frequency of colonic T_{regs}, and, more specifically, of Helios$^-$ T_{regs}; the proportion of Helios$^+$Gata3$^+$ T_{regs} was correspondingly increased (Fig. 3E and fig. S7B).

We noted that the loss of Rorγ$^+$ T_{regs} in *Foxp3-cre.Rorc$^{fl/fl}$* mice led to increased production of IL-17 and interferon-γ (IFN-γ) but not T_H2 cytokines like IL-5 or IL-13, by T_{conv} cells in colons of otherwise unchallenged mice (Fig. 4A), which suggested a decreased ability of colonic T_{regs} lacking Rorγ to regulate inflammatory responses. We thus assessed *Foxp3-cre.Rorc$^{fl/fl}$* mice in the trinitrobenzenesulfonic acid (TNBS)–induced colitis model and found an exacerbation of disease severity, in colitis score and histopathology (Fig. 4, B and C). Furthermore, after TNBS challenge of GF mice monocolonized with different microbes, the frequency of Rorγ$^+$ T_{regs} correlated with the colitis score (Fig. 4D). These results imply a nonredundant role for Rorγ and Rorγ$^+$ T_{regs} in colonic homeostasis.

Thus, Rorγ contributes unexpectedly but in an important way to the T_{reg} response to commensal microbes. This role contrasts with the accepted dichotomy between FoxP3 and Rorγ, a notion stemming mainly from their antagonism in vitro (*14*, *26*–*28*); perhaps this relation has been overinterpreted. There had been indications that the two TFs are not incompatible (*19*), but the present data suggest a collaborative transcriptional impact, consistent with the overlap between their chromatin-binding sites (*29*). The context-specificity of Rorγ's transcriptional footprint is in line with its broad involvement in many immunological and nonimmunological processes (organogenesis, circadian rhythm, and lipid metabolism) (*15*, *30*). Rorγ-dependent *Il23r* expression in T_{regs} also raises the intriguing speculation that human *IL23R* genetic variants associated with inflammatory bowel disease (*31*) might involve balancing effects in effector and regulatory T cells.

Rorγ$^+$ T_{regs} form the majority of the Helios$^-$ T_{regs} that differentiate locally in response to antigens of commensal microbes in the gut (*6*) and do not respond to the alarmin IL-33, in contrast to Gata3$^+$Helios$^+$ cells that expand during tissue damage (*17*, *18*). Mutually exclusive expression of Gata3 and Rorγ in colonic T_{regs} suggests that they may distinguish T_{reg} responses to symbiotic (Rorγ) versus aggressive (Gata3) microbes. Contrary to expectations, many individual microbes proved able to elicit Rorγ$^+$ and Helios$^-$ T_{regs}, a property not restricted to *Clostridiae* (*10*). The graded range suggests that several mechanisms may be involved. The molecular mediator of Rorγ$^+$ T_{reg} induction remains elusive but is unlikely to be SCFAs alone. Rorγ$^+$ induction must follow different routes in T_H17 versus colonic T_{regs}, because the best Rorγ$^+$ T_{reg} inducers do not affect SI T_H17 and vice versa.

In conclusion, these studies show Rorγ as a uniquely microbe-responsive factor induced in two different cellular contexts, in response to different microbes, with distinct transcriptional consequences, and with diametrically opposite functional outcomes.

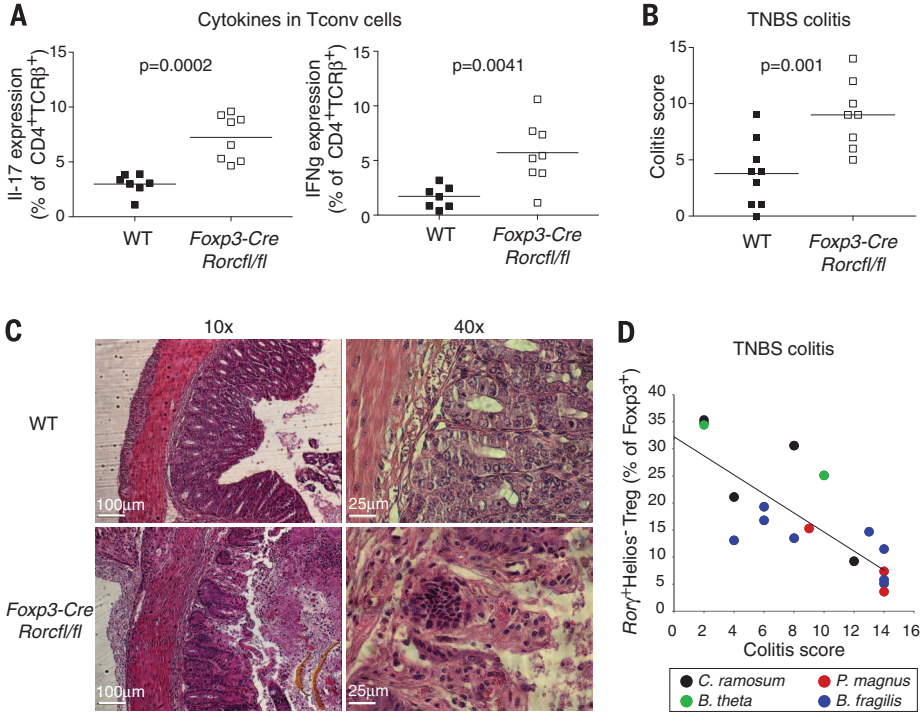


Fig. 4. Rorγ$^+$ T_{regs} control gut inflammation. (**A**) Frequency of IL-17a and IFN-γ expression in Foxp3$^-$CD4$^+$ T_{conv} cells from *Foxp3-cre* × *Rorc$^{fl/fl}$* mice and control *Foxp3-cre* × *Rorc$^{+/+}$* littermates at steady state; *P* values determined by paired Student's *t* test. Each point is an individual mouse. Data are representative of three or more independent experiments. (**B** and **C**) Colitis score (B) and histology (C) of *Foxp3-cre* × *Rorc$^{fl/fl}$* mice and control *Foxp3-cre* × *Rorc$^{+/+}$* littermates challenged with TNBS, calculated on the basis of weight loss, histologic score, and other physical parameters; *P* value as determined by paired Student's *t* test. Each point is an individual mouse. Data representative of more than three independent experiments. (**D**) Correlation between TNBS-colitis score (*x* axis) with frequency of Rorγ$^+$Helios$^-$ within colonic T_{regs} in GF mice monocolonized for 2 weeks with bacteria that elicit different levels of Rorγ$^+$Helios$^-$ T_{regs} before TNBS colitis induction. *B. theta*, *B. thetaiotaomicron*. Pearson's correlation coefficient $r = 0.82$, $P < 0.0001$. Each point is an individual mouse. Data pooled from four experiments.

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SUPPLEMENTARY MATERIALS

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Individual intestinal symbionts induce a distinct population of ROR γ^+ regulatory T cells

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Editor's Summary

Gut microbes make T cells keep the peace

Our guts harbor trillions of microbial inhabitants, some of which regulate the types of immune cells that are present in the gut. For instance, *Clostridium* species of bacteria induce a type of T cell that promotes tolerance between the host and its microbial contents. Ohnmacht *et al.* and Sefik *et al.* characterized a population of gut regulatory T cells in mice, which required gut microbiota to survive. Multiple bacterial species of the microbiota could induce transcription factor–expressing regulatory T cells that helped maintain immune homeostasis. Mice engineered to lack these transcription factors exhibited enhanced susceptibility to colonic inflammation and had elevated amounts of proinflammatory molecules associated with allergies (see the Perspective by Hegazy and Powrie).

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