Acute Gastrointestinal Infection Induces Long-Lived Microbiota-Specific T Cell Responses

Timothy W. Hand,[1] Liliane M. Dos Santos,[1,2] Nicolas Bouladoux,[1] Michael J. Molloy,[1] Antonio J. Pagán,[3] Marion Pepper,[3,4] Craig L. Maynard,[5] Charles O. Elson III,[6] Yasmine Belkaid[1]*

The mammalian gastrointestinal tract contains a large and diverse population of commensal bacteria and is also one of the primary sites of exposure to pathogens. How the immune system perceives commensals in the context of mucosal infection is unclear. Here, we show that during a gastrointestinal infection, tolerance to commensals is lost, and microbiota-specific T cells are activated and differentiate to inflammatory effector cells. Furthermore, these T cells go on to form memory cells that are phenotypically and functionally consistent with pathogen-specific T cells. Our results suggest that during a gastrointestinal infection, the immune response to commensals parallels the immune response against pathogenic microbes and that adaptive responses against commensals are an integral component of mucosal immunity.

The intestinal microbiome is essential to multiple aspects of host physiology (*1*). Recent studies have estimated that the human microbiome contains ~3×10^6 distinct genes each of which may possess multiple antigens (*2*). Regulating immune responses to this extraordinarily diverse set of antigens is a formidable task because commensals also express inflammatory pathogen-associated molecular patterns (PAMPs) that could potentially activate the host immune response (*3*). To limit contact with the commensal microbiota, the gut is compartmentalized and contains various innate and adaptive mechanisms that prevent adaptive immune responses against food and commensal antigens (*4*–*6*). Maintaining

[1]Mucosal Immunology Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Disease, National Institutes of Health (NIH), Bethesda, MD 20892, USA. [2]Laboratory of Gnotobiology and Immunology, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais 31270-901, Brazil. [3]Microbiology, Immunology and Cancer Biology Program, University of Minnesota, Minneapolis, MN 55455, USA. [4]Department of Immunology, University of Washington, Seattle, WA 98195, USA. [5]Department of Pathology, University of Alabama–Birmingham, Birmingham, AL 35294, USA. [6]Mucosal HIV and Immunobiology Center, University of Alabama–Birmingham, Birmingham, AL 35294, USA.

*To whom correspondence should be addressed. E-mail: ybelkaid@niaid.nih.gov

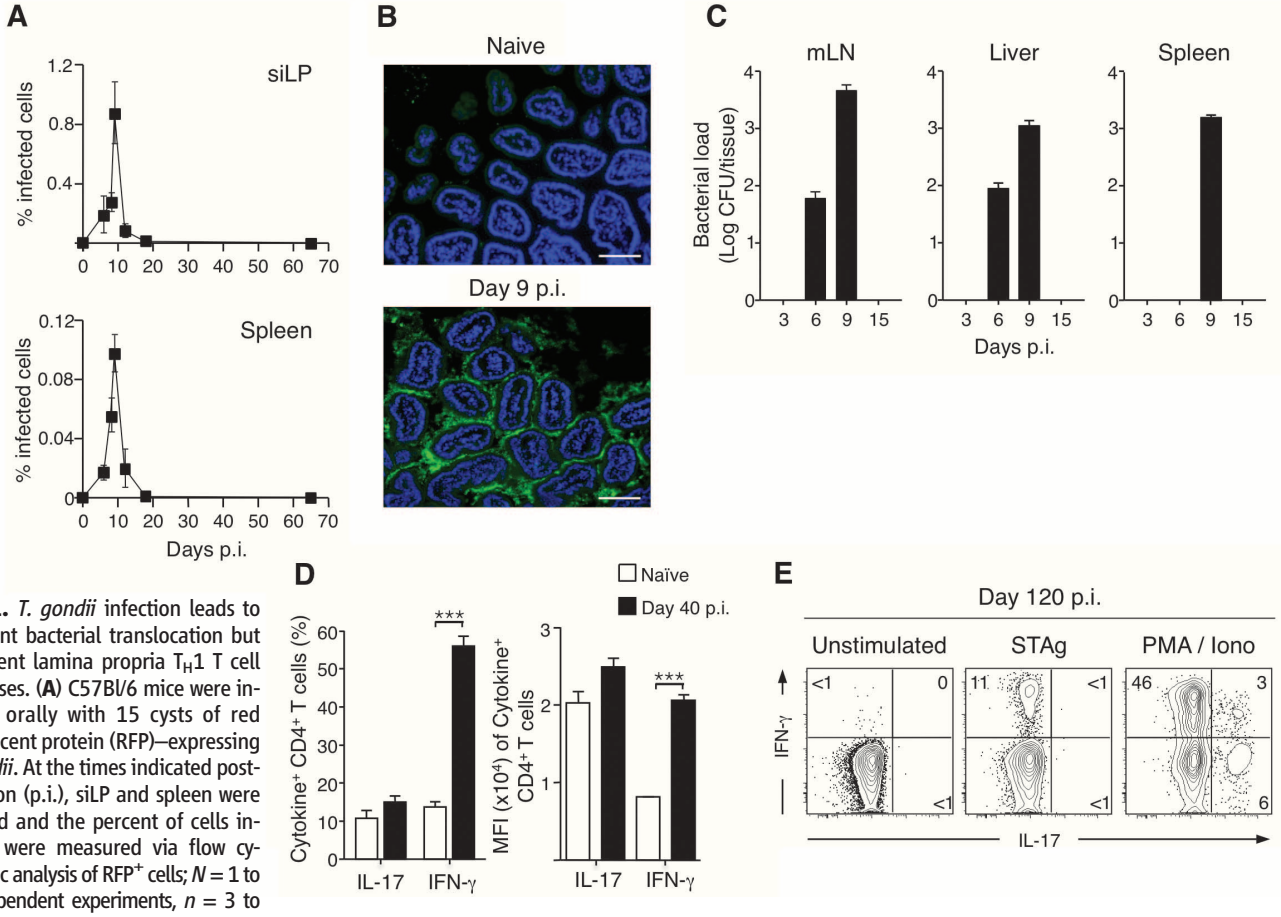


Fig. 1. *T. gondii* infection leads to transient bacterial translocation but persistent lamina propria T_H1 T cell responses. (**A**) C57Bl/6 mice were infected orally with 15 cysts of red fluorescent protein (RFP)–expressing *T. gondii*. At the times indicated post-infection (p.i.), siLP and spleen were isolated and the percent of cells infected were measured via flow cytometric analysis of RFP^+ cells; $N = 1$ to 8 independent experiments, $n = 3$ to 15 mice per time point. (**B**) Small intestinal samples were isolated from naïve and day 9 *T. gondii*–infected mice. Intestinal samples were then fixed, sectioned, counter-stained with 4′,6-diamidino-2-phenylindole (DAPI) and hybridized for FISH with a fluorescent probe specific to eubacterial 16*S* chromosomal sequences. Scale bar, 25 μM; $N = 7$ independent experiments. (**C**) Counts of bacterial colonies cultured from spleen, mesenteric lymph node (mesLN), and liver at time points indicated after *T. gondii* infection; $N = 3$ independent experiments, $n = 3$ to 4 mice per time point. (**D**) Lymphocytes were prepared from the siLP of naïve or day-40 infected mice, stimulated with phorbol 12-myristate 13-acetate (PMA)/ionomycin and stained intracellularly for IFN-γ and IL-17. Bar graph shows the percent (left) or the mean fluorescence intensity (right) of $CD4^+$ cells expressing IFN-γ or IL-17. Shown is a representative example of three separate experiments; $n = 4$ to 6 mice per experiment. (**E**) CD4 T cells were purified from the siLP by means of flow cytometry and cocultured with bone marrow–derived DCs preloaded with soluble *T. gondii* antigen (STAg) or activated with PMA/ionomycin for 3.5 hours. Stimulated cells were stained intracellularly for IFN-γ and IL-17 and analyzed by means of flow cytometry. Shown is one of two experiments. Flow cytometry of CD4 cells is gated Live $TCR\beta^+$ $CD4^+$ $Foxp3^-$. Graphs show mean ± SEM. ***$P < 0.001$.

immune tolerance to commensal–derived antigens in the gastrointestinal (GI) tract is critical because activated CD4 T cells have been strongly associated with inflammatory bowel disease (IBD) (*7*, *8*).

The GI tract is a common site of infection, and whether the immune system discriminates commensals from pathogens is unclear. In some instances, the proinflammatory properties of the microbiota directly contribute to the induction of immune responses and pathogenesis of mucosal infection (*9*–*11*). Whether acute GI infection also leads to priming of adaptive immune responses against commensals has not been addressed. To investigate the fate of immune responses to commensal bacteria after infection, we used *Toxoplasma gondii*. Upon oral infection, *T. gondii* expands systemically in the spleen and locally in the small intestine lamina propria (siLP), where it induces substantial immunopathology that is associated with a T helper 1 (T_H1) immune response and a reduction in regulatory T cells (T_{reg} cells) (Fig. 1A and fig. S1) (*12*). After day 9 of infection, the immune response largely eliminates the parasite from all tissues except the central nervous system and skeletal muscle, where *T. gondii* are encysted in an inactive state (Fig. 1A) (*13*). Oral *T. gondii* infection also leads to an increased association between the commensal bacteria and the intestinal epithelium (Fig. 1B) (*10*). Moreover, bacteria escape the gut and translocate to the mesenteric lymph nodes, liver, and spleen (Fig. 1C). We postulated that immune ignorance of the microbiota may be lost during *T. gondii* infection as a result of bacterial translocation and impaired immune regulation.

Although the gut heals after clearance of *T. gondii*, the siLP harbored a significantly higher frequency of interferon-γ (IFN-γ^+) CD4 T cells as compared with that of naïve mice, whereas the frequency of interleukin 17A (IL-17A)–expressing T cells remained unchanged (Fig. 1D). As expected, a fraction of these cells (~10% of CD4 T cells) were *T. gondii*–specific (Fig. 1E). However, CD4 T cells making IFN-γ in response to nonspecific stimulation far outnumbered those responding to *T. gondii*–derived antigens (~45% of CD4 T cells), implying that a proportion of these cells may be specific to commensal bacteria (Fig. 1E).

To circumvent the high diversity of commensal antigens, we used a T cell receptor (TCR) transgenic mouse specific to a commensal-derived flagellin (CBir1 Tg), expressed by a subset of the Clostridium XIVa cluster of bacteria (CBir1) (fig. S2) (*14*, *15*). CBir1 is clinically relevant because antibodies to CBir1 flagellin are associated with Crohn's disease (*16*). Because of the segregation imposed by the mucosal firewall, splenic T cells from CBir1 Tg mice remain largely naïve (fig. S3) (*15*). Upon transfer into *T. gondii*–infected hosts, CBir1 Tg T cells proliferated extensively, whereas T cells that had been transferred into uninfected hosts remained undivided (Fig. 2, A and B). Thus, T cells specific to commensal-derived antigens proliferate during a heterologous GI infection.

We next addressed whether commensal-specific T cells would differentiate to become effector cells during GI infection. After *T. gondii* infection, CBir1 Tg T cells on WT or $Rag^{-/-}$ background differentiated toward a T_H1 phenotype, as demonstrated by the expression of the canonical transcription factor T-bet (Fig. 2, C and D, and fig. S4). On the other hand, ovalbumin-specific OT-II TCR transgenic cells that had been transferred into *T. gondii*–infected mice remained naïve, and CBir1 Tg T cells did not respond to direct stimulation with *T. gondii* antigens, indicating that CBir1 Tg T cell responses rely on cognate antigen recognition (Fig. 2, E and F, and fig. S5).

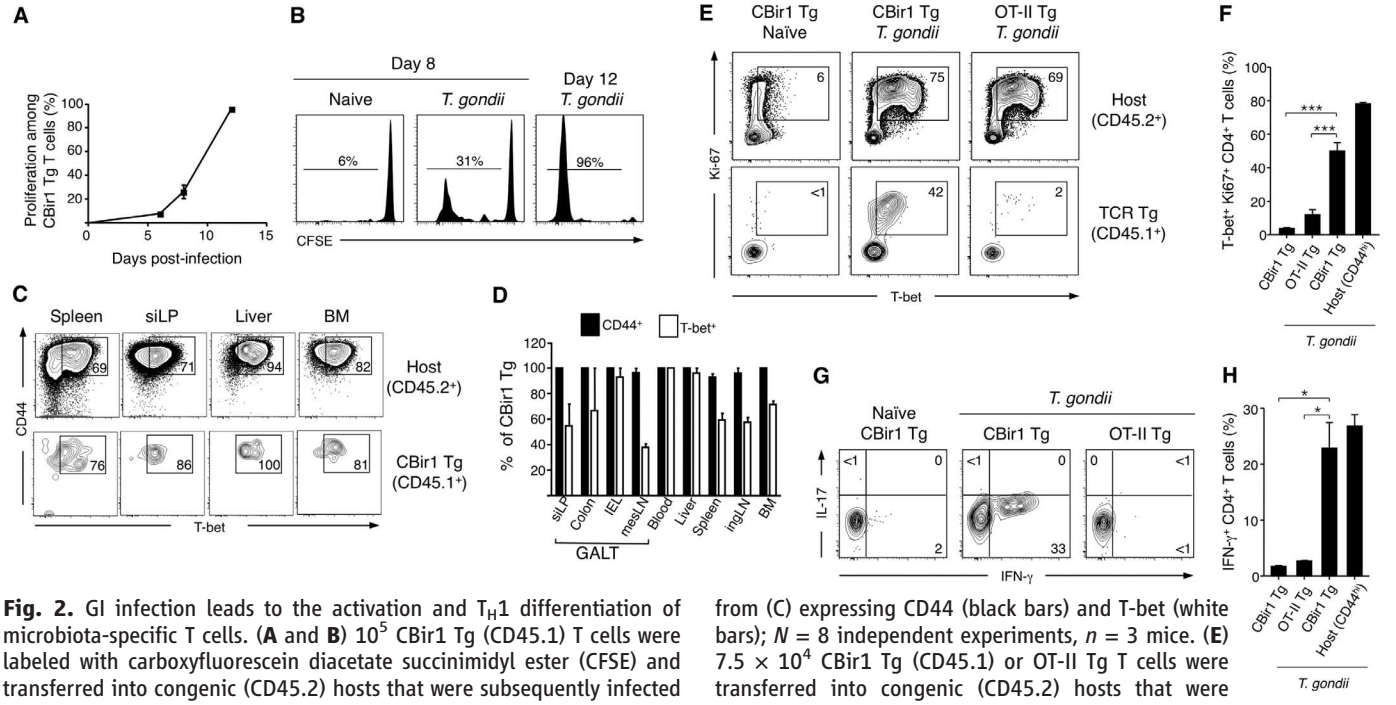


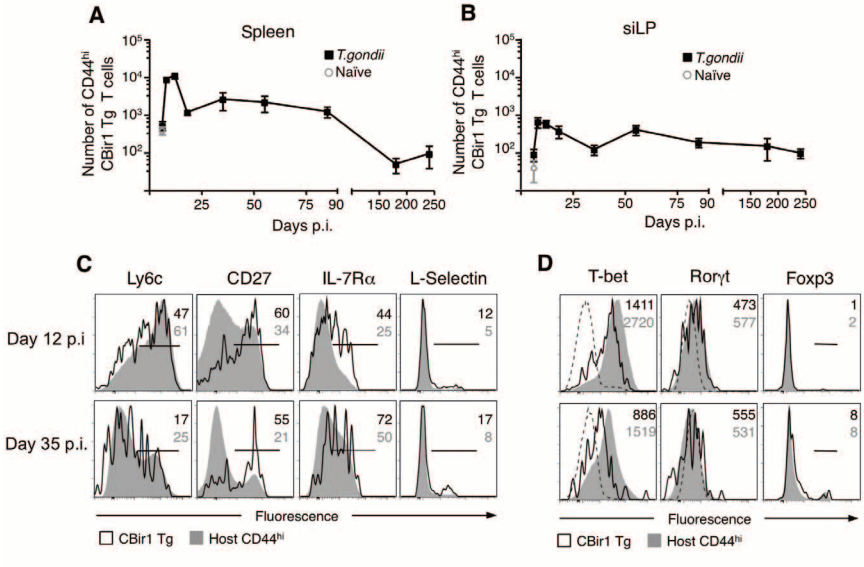
Fig. 2. GI infection leads to the activation and T_H1 differentiation of microbiota-specific T cells. (**A** and **B**) 10^5 CBir1 Tg (CD45.1) T cells were labeled with carboxyfluorescein diacetate succinimidyl ester (CFSE) and transferred into congenic (CD45.2) hosts that were subsequently infected orally with 15 cysts of *T. gondii*. At 6, 8, or 12 days after infection, splenocytes were isolated, and the dilution of CFSE on CBir1 Tg T cells (Live $TCR\beta^+$ $CD4^+$ $CD45.1^+$) was assessed by means of flow cytometry; $n = 3$ to 4 mice per time point. (**C**) 7.5×10^4 CBir1 Tg (CD45.1) T cells were transferred into congenic (CD45.2) hosts that were subsequently infected orally with 15 cysts of *T. gondii*. Eighteen days after infection, single-cell suspensions were prepared from the spleen, ingLN, mesLN, bone marrow, liver, peripheral blood, siLP, intraepithelial lymphocytes, and colon and stained intracellularly for flow cytometry. Contour plots show expression of CD44 and T-bet among CBir1 Tg (CD45.1) CD4 T cells (bottom row) and host $CD4^+$ T cells. (**D**) Bar graph showing the frequency of CBir1 Tg T cells from (C) expressing CD44 (black bars) and T-bet (white bars); $N = 8$ independent experiments, $n = 3$ mice. (**E**) 7.5×10^4 CBir1 Tg (CD45.1) or OT-II Tg T cells were transferred into congenic (CD45.2) hosts that were subsequently infected orally with 15 cysts of *T. gondii* or left naïve. Eight days after infection, splenocytes were isolated and stained intracellularly for flow cytometry. Flow cytometric analysis of T-bet and Ki67 in CBir1 Tg or OT-II Tg (bottom row) and host $CD44^{hi}$ CD4 T cells (top row) is shown. Shown is a representative example of eight separate experiments. (**F**) Quantification of (E). (**G**) Splenocytes from (E) were stimulated with PMA/ionomycin, stained intracellularly for IFN-γ and IL-17, and analyzed by means of flow cytometry. (**H**) Quantification of (G). Data are representative of three separate experiments. All flow cytometry plots in this figure are gated on Live $TCR\beta^+$ $CD4^+$ $Foxp3^-$. Graphs show mean ± SEM; $^*P < 0.05$, $^{***}P < 0.001$.

Activated commensal-specific T cells produced IFN-γ in response to ex vivo stimulation and were observed in all tissues examined, indicating that anti-commensal T cell responses are systemic and functional (Fig. 2, C, D, G, and H; and fig. S6). Taken together, our data show that during GI infection CD4 T cell ignorance of commensal antigens is lost, and microbiota-specific T cells respond in a manner comparable with pathogen-specific T cells.

Under homeostatic conditions, the commensal microbiota can drive the differentiation of T_{reg} and T_H17 cells (*11*, *17*–*21*). However, CBir1 Tg T cells did not induce the expression of IL-17A or the transcription factors Rorγt or Foxp3 during *T. gondii* infection (Figs. 2G and 3D), indicating that microbiota-specific T cells are differentiating according to signals provided by the inflammatory milieu that are not typically present at steady state. Supporting this hypothesis, we found that CBir1 Tg T cells activated during chemical disruption of the GI tract by dextran sodium sulfate (DSS) did not up-regulate T-bet but instead expressed Rorγt (fig. S7).

Immunological memory is a cardinal property of the adaptive immune system allowing for long-term protection against reinfection. During acute infections, T_H1 T cell responses persist after the clearance of the pathogen but slowly decay over time (*22*, *23*). Whether microbiota-specific effector T cells persist as memory cells is a critical question. Assessment of CBir1 Tg T cell response revealed that the number of effector ($CD44^{hi}$) CBir1 Tg T cells expanded ~10-fold from day 6 to the peak of the anti-microbiota response at day 12 after infection in both the spleen and siLP (Fig. 3, A and B). In accordance with what has been observed for pathogen-specific CD4 T cell responses, CBir1 Tg T cells contracted after day 12 of infection (Fig. 3, A and B) (*22*, *23*). However, small populations of $CD44^{hi}$ CBir1 Tg T cells can be identified from both the spleen and lamina propria up to 240 days after infection, indicating that microbiota-specific cells generated in the context of heterologous GI infection have the potential for long-term survival (Fig. 3, A and B). T_H1 CD4 T cells with increased potential to survive and form memory can be separated from terminally differentiated cells by the characteristic expression of CD27 and low expression of Ly6c and T-bet (*23*–*25*). Strikingly commensal-specific T cells largely differentiate to a phenotype consistent with long-lived T_H1 memory T cells (Fig. 3, C and D). Critically, survival of memory CBir1 Tg cells was not the consequence of continuous antigen exposure because naïve CBir1 Tg T cells that had been transferred into mice 90 days after infection with *T. gondii* did not respond (fig. S8). In order to control for possible artifacts associated with the transfer of transgenic T cells, we examined the endogenous anti-CBir1 flagellin response via a major histocompatibility complex class II multimer (*26*, *27*). In agreement with our T cell transfer studies, the majority of CBir1 multimer–positive cells in specific pathogen- and germ-free mice were naïve ($CD44^{lo}$) (Fig. 3, E and F). In contrast, 75 days after *T. gondii* infection the majority of CBir1-specific cells displayed an activated ($CD44^{hi}$) phenotype, indicating that the endogenous population of CBir1-specific cells is activated after GI infection and survives long-term as memory cells (Fig. 3, E and F, and fig. S9). In accordance with results obtained with transferred CBir1 Tg T cells, $CD44^{hi}$ CBir1 tetramer–specific cells expressed lower levels of Ly6c and increased amounts of CD27 than did *T. gondii*–specific cells from the same time point of infection (fig. S10). The majority of CBir1-specific T cells was also activated in mice treated with DSS, highlighting the importance of GI tract integrity in maintenance of CD4 T cell ignorance to commensal antigens (Fig. 3, E and F). Therefore, commensal-specific T cells activated during GI infection survive long-term and persist in extralymphoid tissue in a manner consistent with that of pathogen-specific memory cells.

A fundamental property of memory T cells is the ability to proliferate rapidly and elicit effector functions in response to secondary challenge. Indeed, CBir1 Tg T cells were able to rapidly make IFN-γ and IL-2 in response to stimulation with specific peptide 75 days after infection (fig. S11). To test whether persisting commensal-specific T cells also maintain proliferative potential, we infected mice carrying CBir1 Tg T cells then rechallenged the mice with CBir1 peptide 35 days



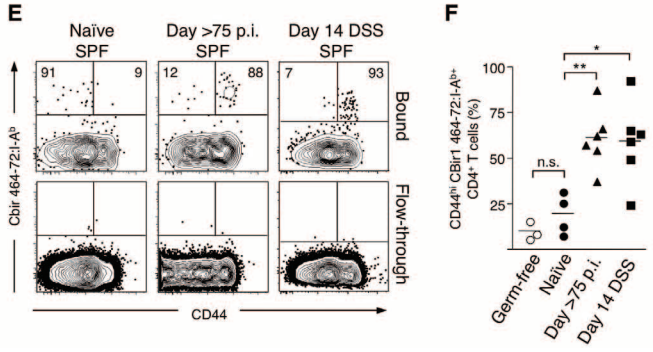


Fig. 3. GI infection induces microbiota-specific memory CD4 T cells. (**A** and **B**) 7.5×10^4 CBir1 Tg (CD45.1) T cells were transferred into congenic (CD45.2) hosts that were subsequently infected orally with 15 cysts of *T. gondii*. At the days indicated, splenocytes (A) and siLP cells (B) were isolated, and the number of $CD44^{hi}$ CBir1 Tg T cells (black squares) in each tissue was assessed by means of flow cytometry. Open gray circle shows the number of CD44hi CBir1 Tg T cells in naïve mice 8 days after transfer of CBir1 Tg T cells; $N = 1$ to 8 independent experiments, $n = 3$ to 15 mice per time point. (**C**) Flow cytometric analysis of surface marker phenotype of transferred CBir1 Tg T cells (CD45.1) (black line) and host CD44hi T cells (CD45.2) (gray shaded) at day 12 and day 35 after infection isolated from the spleen. (**D**) Expression of transcription factors in CBir1 Tg T cells (CD45.1) (black line) and host CD44hi T cells (CD45.2) (gray shaded) at day 12 and day 35 after infection isolated from the spleen. Histograms in (C) and (D) are gated on Live $TCR\beta^+$ $CD4^+$; data shown is representative of three separate experiments. (**E**) Flow cytometric analysis of $CBir_{464–72}$:$I\text{-}A^b$ tetramer–binding populations from the total secondary lymphoid tissue in naïve, after-day-75 *T. gondii*–infected and DSS-treated mice. The top row depicts the population bound during tetramer-specific separation; the bottom row shows the nonbinding column flow-through to show specificity. Plots are gated on $DAPI^-$ $NK1.1^-$ $F4/80^-$ $CD11c^-$ $CD11b^-$ $B220^-$ $CD3^+$ $CD4^+$. (**F**) Bar graph shows the percent $CD44^{hi}$ of CBir464_72:$I\text{-}A^b$ tetramer–binding cells in germ-free (open circles), naïve (solid circles), infected (triangles), and DSS-treated (squares) mice. Data from (E) are representative of three experiments. Graphs show mean ± SEM; $*P < 0.05$, $**P < 0.01$.

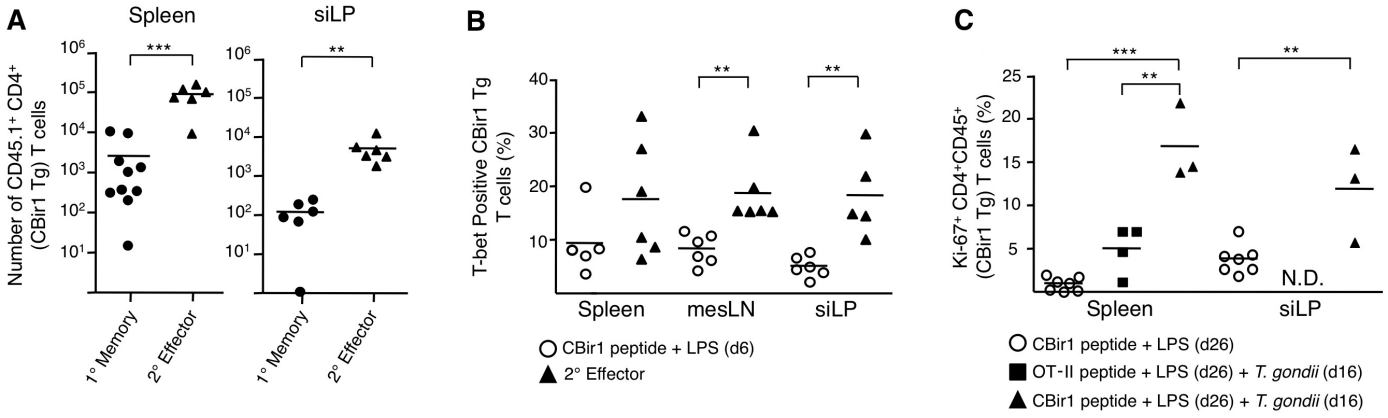


Fig. 4. Microbiota-specific memory T cell are functional and can be reactivated by GI infection. (**A**) 7.5×10^4 CBir1 Tg (CD45.1) T cells were transferred into congenic (CD45.2) hosts that were subsequently infected orally with 15 cysts of *T. gondii*. Thirty-five days after infection with *T. gondii*, mice carrying CBir1 Tg T cells were injected with CBir1 peptide and LPS. Numbers are of CBir1 Tg T cells (CD45.1) in the spleen and siLP at day 35 (1° memory) or 6 days after stimulation with CBir peptide and LPS (2° effector). Shown is a composite of three experiments. (**B**) Either naïve hosts carrying ~10^4 naïve CBir1 Tg T cells (open circles) or day 35 (1° memory) *T. gondii*–infected mice (black triangles) were injected with CBir peptide and LPS as in (A). Six days after injection, splenocytes were isolated and stained intracellularly for T-bet. Data shown is representative of three experiments. (**C**) Naïve hosts carrying ~10^4 naïve CBir1 Tg or OT-II Tg T cells were injected with peptide and LPS. Ten days after immunization, these mice were infected with 15 cysts *T. gondii*. Shown are percent Ki67$^+$ CBir1 Tg T cells isolated from the spleen and siLP from mice 16 days after infection (26 days post-immunization). Data shown are representative of three separate experiments. CBir1 Tg T cells are gated Live TCRβ^+ CD4$^+$ Foxp3$^-$ CD45.1$^+$. Graphs show mean ± SEM; $^{**}P < 0.01$, $^{***}P < 0.001$.

later. Before peptide challenge, CBir1 Tg T cells were uniformly activated (fig. S12). Memory CBir1 Tg T cells proliferated after antigen-specific challenge and accumulated in both the spleen and siLP (34- and 42-fold expansion, respectively) (Fig. 4A). In comparison with naïve CBir1 Tg T cells after activation with peptide and lipopolysaccharide (LPS), memory CBir1 Tg T cells maintained a significant level of expression of T-bet and had notably reduced expression of IL-7Rα (Fig. 4B and fig. S13). Therefore after recall, commensal-specific memory cells have a phenotype distinct from primary effectors and associated with their previous polarization. We next tested whether an established commensal-specific T cell population could be reactivated by GI infection. To address this point, we activated naïve CBir1 Tg T cells in vivo with peptide and LPS, waited for the primary immune response to subside, and then infected mice with *T. gondii*. Secondary infection induced proliferation of a fraction of CBir1 Tg T cells in both the siLP and spleen, as indicated by expression of Ki67 (Fig. 4C). Thus, activated commensal-specific T cells can proliferate in response to infectious rechallenge.

The GI tract represents a major site of exposure to pathogens, and our results propose that these pathogenic exposures lead to long-lived anticommensal immunity (*28*, *29*). In support of this hypothesis, healthy human serum contains antibodies specific to the intestinal microbiota (*30*). Because of the abundance of commensal antigens, a fraction of the memory CD4 T cell population induced in response to GI infection is likely composed of various commensal-specific clones that together may constitute a substantial population. Further, our results suggest that primary immune responses to GI infections occur in the context of broader secondary responses against commensals. Several genes involved in sustaining the intestinal barrier and CD4 function have been associated with IBD, and in the context of such mutations, regulation of activated commensal-specific T cells could be jeopardized, leading to immunopathology (*7*). Indeed, GI barrier dysfunction and infection have been shown to synergize to induce IBD (*31*). Because bacteria colonize all pathogen entryways, such as the skin, lung, and GI tract, our findings raise the question of whether immunity and inflammation at barrier sites is generally controlled by responses to commensals.

References and Notes

1. A. L. Kau, P. P. Ahern, N. W. Griffin, A. L. Goodman, J. I. Gordon, *Nature* **474**, 327 (2011).
2. J. Qin *et al.*, MetaHIT Consortium, *Nature* **464**, 59 (2010).
3. A. Iwasaki, R. Medzhitov, *Nat. Immunol.* **5**, 987 (2004).
4. A. J. Macpherson, E. Slack, M. B. Geuking, K. D. McCoy, *Semin. Immunopathol.* **31**, 145 (2009).
5. A. J. Macpherson, T. Uhr, *Science* **303**, 1662 (2004).
6. E. Slack *et al.*, *Science* **325**, 617 (2009).
7. A. Franke *et al.*, *Nat. Genet.* **42**, 1118 (2010).
8. A. Kaser, S. Zeissig, R. S. Blumberg, *Annu. Rev. Immunol.* **28**, 573 (2010).
9. A. Benson, R. Pifer, C. L. Behrendt, L. V. Hooper, F. Yarovinsky, *Cell Host Microbe* **6**, 187 (2009).
10. M. M. Heimesaat *et al.*, *J. Immunol.* **177**, 8785 (2006).
11. I. I. Ivanov *et al.*, *Cell* **139**, 485 (2009).
12. G. Oldenhove *et al.*, *Immunity* **31**, 772 (2009).
13. M. Munoz, O. Liesenfeld, M. M. Heimesaat, *Immunol. Rev.* **240**, 269 (2011).
14. L. W. Duck *et al.*, *Inflamm. Bowel Dis.* **13**, 1191 (2007).
15. Y. Cong, T. Feng, K. Fujihashi, T. R. Schoeb, C. O. Elson, *Proc. Natl. Acad. Sci. U.S.A.* **106**, 19256 (2009).
16. M. J. Lodes *et al.*, *J. Clin. Invest.* **113**, 1296 (2004).
17. K. Atarashi *et al.*, *Science* **331**, 337 (2011).
18. V. Gaboriau-Routhiau *et al.*, *Immunity* **31**, 677 (2009).
19. M. B. Geuking *et al.*, *Immunity* **34**, 794 (2011).
20. S. K. Lathrop *et al.*, *Nature* **478**, 250 (2011).
21. M. Lochner *et al.*, *J. Immunol.* **186**, 1531 (2011).
22. L. E. Harrington, K. M. Janowski, J. R. Oliver, A. J. Zajac, C. T. Weaver, *Nature* **452**, 356 (2008).
23. M. Pepper *et al.*, *Nat. Immunol.* **11**, 83 (2010).
24. H. D. Marshall *et al.*, *Immunity* **35**, 633 (2011).
25. F. Sallusto, A. Lanzavecchia, *Eur. J. Immunol.* **39**, 2076 (2009).
26. J. J. Moon *et al.*, *Immunity* **27**, 203 (2007).
27. J. Hataye, J. J. Moon, A. Khoruts, C. Reilly, M. K. Jenkins, *Science* **312**, 114 (2006).
28. M. Kosek, C. Bern, R. L. Guerrant, *Bull. World Health Organ.* **81**, 197 (2003).
29. L. Vernacchio *et al.*, *Pediatr. Infect. Dis. J.* **25**, 2 (2006).
30. A. Haas *et al.*, Swiss HIV Cohort Study, *Gut* **60**, 1506 (2011).
31. K. Cadwell *et al.*, *Cell* **141**, 1135 (2010).

Acknowledgments: This work was supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases (NIAID) (T.W.H., L.M.D., N.B., M.J.M., and Y.B.), CNPq-Brazil (L.M.D.), NIH grants DK071176 and DK64400 (C.O.E.) and The Crohn's and Colitis Foundation of America Career Development Award (C.L.M.). The authors thank M. Jenkins, A. Poholek, S. Kaech, N. Peters, J. Monteiro and the members of the Belkaid Lab for critical discussion and reading of the manuscript; the NIH Tetramer Core Facility for the *T. gondii* Me49 hypothetical protein tetramers; C. Eigsti, T. Moyer, E. Stregevsky, K. Holmes, and the NIAID Flow Cytometry Core for assistance with sorting; L. Koo and the NIAID Microscopy Core for assistance with 16*S* fluorescence in situ hybridization (FISH) images; and the NIAID Protein Biochemistry Core for CBir1 peptide. We thank the University of Alabama–Birmingham for sharing the CBir1 Tg mice by material transfer agreement. The data reported in this paper are tabulated in the main text and in the supplementary materials. The authors declare that they have no conflict of interest.

Supplementary Materials

www.sciencemag.org/cgi/content/full/science.1220961/DC1
Materials and Methods
Figs. S1 to S13

23 February 2012; accepted 13 July 2012
Published online 23 August 2012;
10.1126/science.1220961

Science

Acute Gastrointestinal Infection Induces Long-Lived Microbiota-Specific T Cell Responses

Timothy W. Hand, Liliane M. Dos Santos, Nicolas Bouladoux, Michael J. Molloy, Antonio J. Pagán, Marion Pepper, Craig L. Maynard, Charles O. Elson III, and Yasmine Belkaid

Science, 337 (6101), • DOI: 10.1126/science.1220961

Recognizing Escaped Commensals

In order to coexist peacefully, the billions of bacteria in our gut and our immune system have reached a détente. An intestinal mucosal firewall exists, so bacteria remain localized to the gut, where the immune system is tightly regulated so that these bacteria are tolerated. Enteric infections, however, lead to a breach in this mucosal firewall, resulting in exposure of the peripheral immune system to the intestinal bacterial contents. What is the result? Using oral *Toxoplasma gondii* infection in mice, Hand *et al.* (p. 1553, published online 23 August) show that, besides the *T. gondii*–specific T cell response, a commensal bacteria–specific T cell response is elicited. The CD4 T cell–specific response was tracked to a commensal-derived flagellin, and these T cells expanded after *T. gondii* infection and formed long-lived memory cells able to respond to subsequent challenges. Thus, enteric infections can lead to the formation of commensal bacteria–specific, long-lived memory T cells that reside throughout the body—which may play a role in intestinal pathologies such as inflammatory bowel disease.

Science (ISSN 1095-9203) is published by the American Association for the Advancement of Science. 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.