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Supplementary Materials
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Interactions Between Commensal Fungi and the C-Type Lectin Receptor Dectin-1 Influence Colitis

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The intestinal microflora, typically equated with bacteria, influences diseases such as obesity and inflammatory bowel disease. Here, we show that the mammalian gut contains a rich fungal community that interacts with the immune system through the innate immune receptor Dectin-1. Mice lacking Dectin-1 exhibited increased susceptibility to chemically induced colitis, which was the result of altered responses to indigenous fungi. In humans, we identified a polymorphism in the gene for Dectin-1 (*CLEC7A*) that is strongly linked to a severe form of ulcerative colitis. Together, our findings reveal a eukaryotic fungal community in the gut (the "mycobiome") that coexists with bacteria and substantially expands the repertoire of organisms interacting with the intestinal immune system to influence health and disease.

Interactions between the commensal microflora and the gut immune system are critical for establishing a balance between immunity and tissue health. Changes in gut bacteria described as "dysbiosis" have been associated with intestinal inflammation (*1*–*3*) and metabolic syndrome (*4*–*6*). The vast majority of studies on commensal microbiota have focused on gut bacteria, and the terms "intestinal microbiota" and "intestinal bacteria" are often used interchangeably. Recent studies have begun to note, however, that a fraction of gut microorganisms are not bacterial (*7*). Although a few studies have suggested the presence of commensal fungi in the gut (*8*, *9*), whether they interact with the mucosal immune system or influence diseases is unknown.

Fungi are recognized by a number of immune receptors among which Dectin-1 has emerged as key for phagocytosis and killing by myeloid phagocytes. Dectin-1 is a C-type lectin receptor that recognizes β-1,3-glucans found in the cell walls of nearly all fungi. Dectin-1 activates intracellular signals through caspase recruitment domain–containing protein 9 (CARD9), which leads to inflammatory cytokine production and induction of T helper 17 (T_H17) immune responses (*10*–*13*). Deficiencies in either Dectin-1 or CARD9 result in enhanced susceptibility to pathogenic fungal infections in humans and mice (*14*–*16*). Polymorphic variants in the gene for CARD9 are strongly associated with Crohn's disease and ulcerative colitis in humans (*17*, *18*). Furthermore, anti–*Saccharomyces cerevisiae* antibodies (ASCA) against yeast mannan have been strongly associated with Crohn's disease (*19*, *20*). Together, these last-named findings suggest a possible link between immune responses to commensal fungi and intestinal disease.

We examined fungal distribution and detected fungal ribosomal DNA (rDNA) throughout the murine gastrointestinal tract with highest densities in the terminal colon of C57BL/6 (Fig. 1A) and 129S2/Sv (fig. S1A) mice. We stained colonic tissue sections and observed that fungi are abundant and in close proximity with commensal bacteria (Fig. 1B and figs. S1B and S2 to S4). Furthermore, we found that a soluble Dectin-1 probe (*21*) binds to 5 to 7% of the fecal material, consisting of fungal cells with various morphologies (Fig. 1C and fig. S5). Fungi were also present in rat, guinea pig, rabbit, pig, dog, and human feces (fig. S1C). Together, the data demonstrate that commensal fungi contribute to the intestinal microbial community in many species.

We next examined whether gut fungi can be detected by the immune system upon intestinal insult. We utilized a mouse model of dextran sodium sulfate (DSS)–induced colitis extended to allow antibody responses to develop. We found that DSS-induced intestinal inflammation led to the development of circulating immunoglobulin G (IgG) and IgM antibodies against fungi (ASCA) (Fig. 1D), which suggested that fungal antigens indigenous to the gut might be responsible for the induction of ASCA during colitis.

Because gut commensal fungi are recognized by Dectin-1, we tested whether Dectin-1–deficient mice (*Clec7a*$^{-/-}$) are susceptible to DSS-induced colitis. *Clec7a*$^{-/-}$ mice experienced increased weight loss (Fig. 2A) and displayed altered histology characterized by increased mucosal erosion, crypt destruction, inflammatory cell infiltration, and tumor necrosis factor–α (TNF-α) production in the colon (Fig. 2, B to D) as compared with their wild-type (WT) littermate controls. We further detected augmented production of interferon-γ (IFN-γ) and interleukin-17 (IL-17) in intestines from *Clec7a*$^{-/-}$ mice (fig. S6). Similar results were obtained comparing cohoused animals (fig. S7). These results indicate that Dectin-1 deficiency leads to increased susceptibility to colitis.

Many studies have documented the importance of bacteria in intestinal inflammation, so we examined whether bacteria could contribute to the susceptible phenotype. We observed no significant differences in major phyla of commensal bacteria between WT and *Clec7a*$^{-/-}$ mice (fig. S8). To directly determine whether microflora can transfer disease, we depleted intestinal bacteria and fungi with antibiotics, transplanted fecal microflora from WT or *Clec7a*$^{-/-}$ mice, and exposed mice to DSS. Microflora from *Clec7a*$^{-/-}$ mice did not transfer susceptibility to disease (Fig. 2, E and F, and figs. S9 and S10). The data demonstrate that the disease phenotype in the *Clec7a*$^{-/-}$ mice is affected by the genotype of the mouse, not by initial differences in microflora.

We know very little about what commensal fungi populate the murine gut or how they con-

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tribute to colitis in Dectin-1 deficiency. To define the mouse intestinal fungal microbiome, we isolated DNA from murine feces, amplified the internal transcribed spacer region (ITS1-2) of fungal rDNA, and performed high-throughput sequencing (*22*). Combining data from 23 mice, we obtained >30 Mb of raw data from 454 pyrosequencing and >2.2 Gb of raw data from Illumina genome analyzer (GA) sequencing, together containing >1.3 million individual sequences that passed quality control. Detailed analysis identified >100 different well-annotated fungal species representing at least 50 genera, which illustrated the fungal diversity. In addition, we identified >100 novel and/or unannotated fungi representing the large uncharacterized nature of the mycobiome in the gut (figs. S11 and S12). Note that 97.3% of all the fungal sequences identified belonged to 10 fungal species, with 65.2% of the sequences belonging to a single fungus: *Candida tropicalis* (Fig. 3A and fig. S13). We found 7 of the 20 most common gut fungi also in mouse food (fig. S13 and S14). These accounted, however, for only 1.5% of total fungi in the intestines, which suggests that highly represented fungal species are indigenous to the gut.

Many studies have shown that intestinal inflammation can lead to changes in commensal bacteria that affect the host (*1*, *2*, *23*). Whether colitis affects the makeup of the commensal mycobiome is unknown. One study has reported increased fungal burden in intestines of Crohn's disease patients (*9*), and another has shown increased colonization with exogenously added *C. albicans* during DSS colitis in mice (*24*). Notably, we found that, during colitis in *Clec7a*$^{-/-}$ mice the proportion of opportunistic pathogenic fungi including *Candida* and *Trichosporon* increases, whereas nonpathogenic *Saccharomyces* decreases (Fig. 3B and fig. S15). Examination of colons revealed that fungi invade inflamed tissues in DSS-treated *Clec7a*$^{-/-}$ mice but remain in the lumen of DSS-treated WT mice (Fig. 3C and fig. S16). These data are consistent with the observation that intestinally conditioned *Clec7a*$^{-/-}$ dendritic cells are less capable of killing *C. tropicalis* in vitro (Fig. 3D). Together, the data suggest that Dectin-1 deficiency leads to altered immunity to commensal fungi in the gut.

Given that *C. tropicalis* is an opportunistic pathogen, we further analyzed its role during

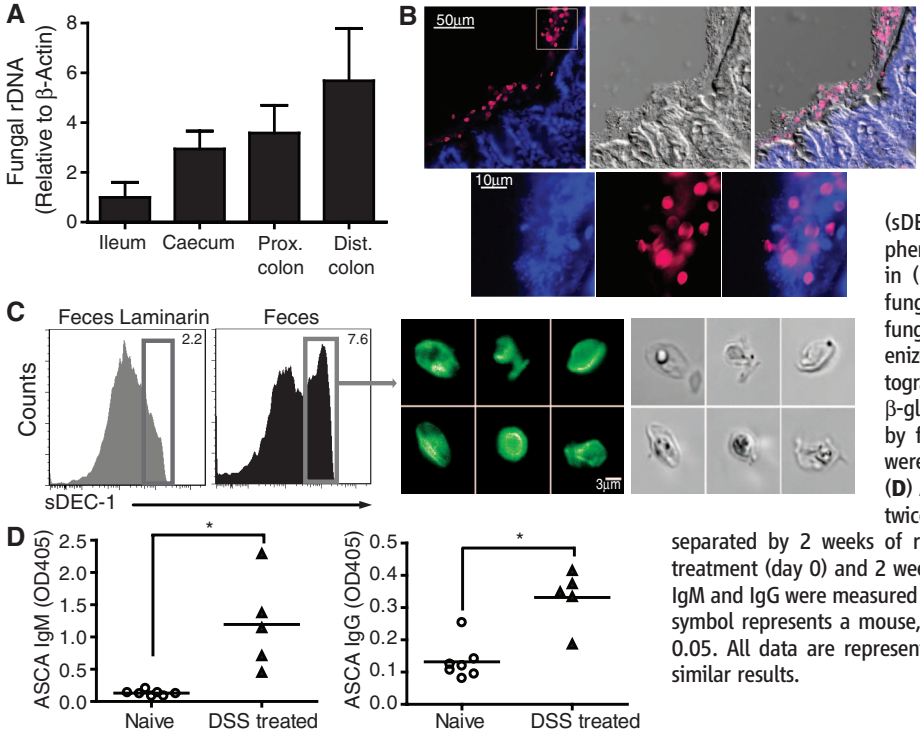

Fig. 1. Commensal fungi are present in the intestine and are recognized by Dectin-1. (**A**) Prevalence of fungi in mucosa isolated from ileum, cecum, proximal (prox) and distal (dist) colon of C57BL/6J mice. ITS1-2 rDNA level was analyzed by quantitative polymerase chain reaction and normalized to β-actin DNA. (**B**) Visualization of commensal fungi in the intestine. Colon sections were stained with a soluble Dectin-1 probe (sDEC-1) and counterstained with 4′,6′-diamidino-2-phenylindole (DAPI). The DAPI signal has been amplified in (B, bottom) to show that DAPI-stained bacteria and fungi are in close proximity to each other. (**C**) Intestinal fungi are recognized by Dectin-1. Fecal pellets were homogenized and labeled with sDEC-1 in the presence (gray histogram) or absence (black histogram) of laminarin (a soluble β-glucan) to block specific binding. Binding was assessed by flow cytometry (left panels). Dectin-1–binding fungi were sorted (right) and visualized by confocal microscopy. (**D**) ASCA generation after DSS colitis. Mice were exposed twice to 2.5% DSS-supplemented water for 7 days each separated by 2 weeks of recovery. Serum samples were collected before DSS treatment (day 0) and 2 weeks after the last DSS cycle (42 days total), and ASCA IgM and IgG were measured by enzyme-linked immunosorbent assay (ELISA). Each symbol represents a mouse, all error bars indicate the SD; unpaired *t* test, $*P < 0.05$. All data are representative of at least two independent experiments with similar results.

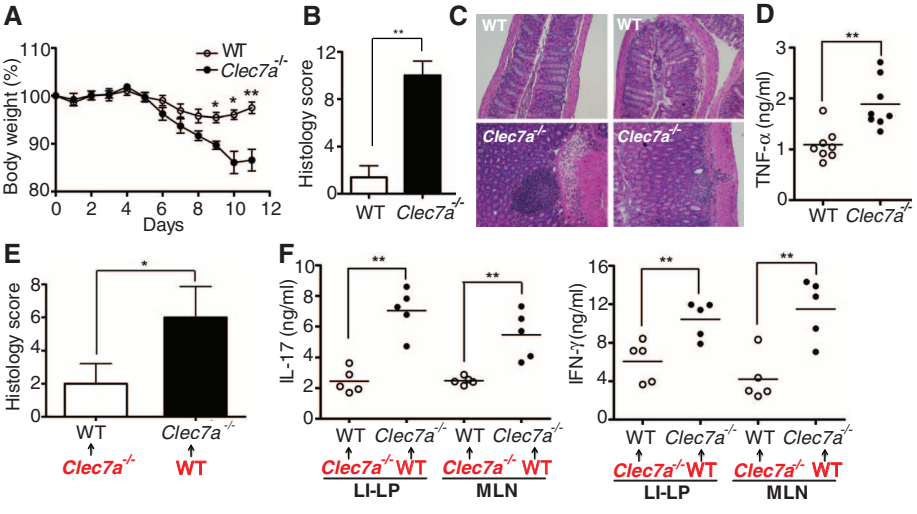

Fig. 2. Dectin-1 regulates the severity of colitis. WT and *Clec7a*$^{-/-}$ littermates were treated with 2.5% DSS for 7 days and kept on water for 4 additional days. Colitis progress and severity were assessed by measuring body weight during treatment (**A**), histology (**B** and **C**), and TNF-α production in the colon (**D**) on day 11. (**E** and **F**) WT and *Clec7a*$^{-/-}$ mice were given an antibiotic cocktail including fluconazole for 3 weeks, given a transplant as indicated (red) with fecal microflora from WT or *Clec7a*$^{-/-}$ mice, and treated with DSS as in (A). Disease severity was accessed by histology score (E) and by cytokine production stimulated by antibodies against CD3 and CD28 in large-intestine lamina propria (LI-LP) and MLN T cells (F). Each symbol represents a different mouse. One of four independent experiments is shown. Error bars, SD; $*P < 0.05$, $**P < 0.01$.

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colitis. We supplemented mice with *C. tropicalis* and subjected them to DSS. (See fig. S17A for dosing schedule.) For comparison, another group of mice was supplemented with *S. fibuligera*, a nonpathogenic fungus that, like *C. tropicalis*, grows in yeast and filamentous forms and is recognized by Dectin-1 (fig. S18). Colitis symptoms including weight loss, crypt loss, and inflammatory cell infiltration were more severe in *Clec7a*$^{-/-}$ mice supplemented with *C. tropicalis* compared with the *Clec7a*$^{-/-}$ controls (Fig. 3E and fig. S17, B and C). In contrast, *C. tropicalis* supplementation did not aggravate colitis in WT mice. Consistent with the pathology, we detected increased IL-17 and IFN-γ production by T cells from the mesenteric lymph nodes (MLNs) and colons of *Clec7a*$^{-/-}$ mice supplemented with *C. tropicalis* (fig. S17, D and E), as well as increased message for TNF-α, IL-23p19, IL-17a, Cxcl2, and defensins in colons (fig. S19). This correlated with higher loads of *C. tropicalis* in the intestines of DSS-treated *Clec7a*$^{-/-}$ mice (fig. S20B). In contrast, *S. fibuligera* supplementation did not contribute to colitis pathology (Fig. 3E and figs. S17 and S19), and fungal loads were unchanged (fig. S20C). The data suggest that an inability of *Clec7a*$^{-/-}$ mice to mount effective immune responses to specific intestinal fungi creates conditions that promote inflammation.

To determine whether the altered fungal burden during colitis contributes to disease severity in the absence of Dectin-1, we suppressed fungal growth with fluconazole, a specific antifungal

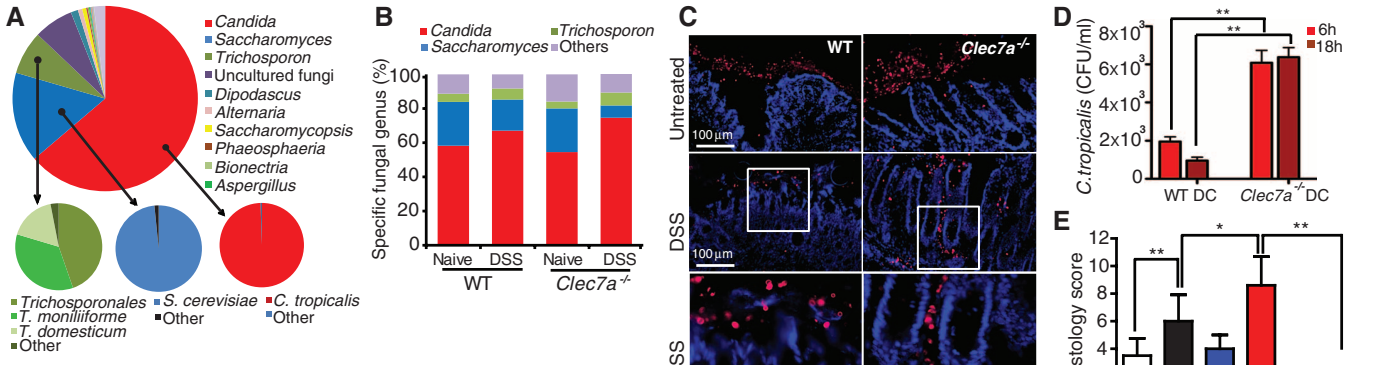
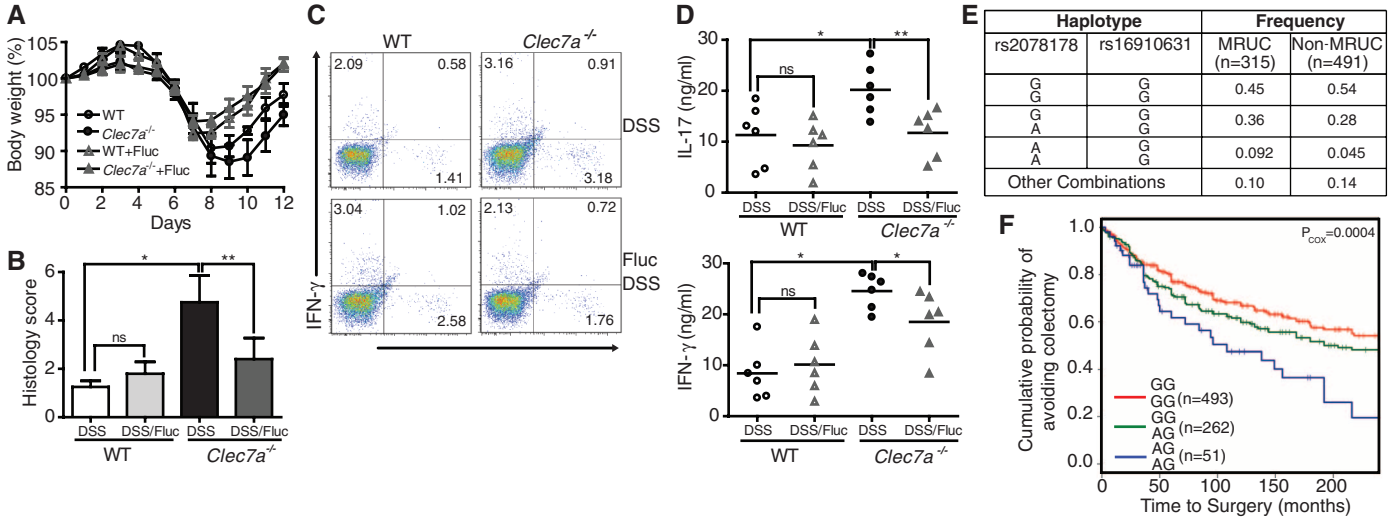


Fig. 3. Defining the fungal microbiome and characterizing the specific role of Dectin-1–mediated host defense during colitis. (**A**) DNA was isolated from murine feces, and mycobiome analysis was performed using Roche 454 and Illumina GA sequencing of ITS1-2 rDNA. The taxonomic distribution of the most abundant fungal genera is shown (large pie chart), and the species breakdowns for major groups are provided (small pie charts). (**B**) Quantitative analysis of the major intestinal fungal genera in WT and *Clec7a*$^{-/-}$ mice before and after treatment with DSS. Illumina GA data were analyzed and presented as relative percentage of dominant fungal genera (n = 16 mice). (**C**) Fungal invasion of colonic tissue in *Clec7a*$^{-/-}$ mice during colitis. Colon sections from WT and *Clec7a*$^{-/-}$ mice before and after colitis were stained with the sDEC-1 probe and counterstained with DAPI. (**D**) Intestinally conditioned dendritic cells were incubated with live *C. tropicalis*, and killing was assessed after 6 and 18 hours. (**E**) Histology score of WT and *Clec7a*$^{-/-}$ mice supplemented or not with four doses of *C. tropicalis* or *S. fibuligera* every other day, and then treated with 2.5% DSS for 7 days and kept on water for 4 additional days. Data are representative of at least two independent experiments with similar results. Error bars, SD; *P < 0.05, **P < 0.01.



Haplotype		Frequency	
rs2078178	rs16910631	MRUC (n=315)	Non-MRUC (n=491)
G G	G G	0.45	0.54
G A	G G	0.36	0.28
A A	G G	0.092	0.045
Other Combinations		0.10	0.14

Fig. 4. Antifungal therapy ameliorates colitis in *Clec7a*$^{-/-}$ mice, and *CLEC7A* associates with UC severity in humans. (**A**) WT and *Clec7a*$^{-/-}$ mice were given fluconazole in their drinking water for total of 14 days (starting 2 days before the induction of DSS colitis), and body weight was measured. Weight loss is shown in (A) (P < 0.05). Histology score (**B**), the percentage of IL-17– and IFN-γ–producing CD4$^+$ T cells in LI-LP (**C**), and IL-17 and IFN-γ production in MLNs (**D**) were determined 4 days after the 7 days of DSS treatment. Each symbol represents a different mouse. One of three independent experiments with similar results is shown. Error bars, SD; *P < 0.05, **P < 0.01. (**E**) Specific *CLEC7A* haplotypes associate with MRUC. Haplotypes were formed from rs2078178 and rs16910631 using PHASE v2.3. Haplotypes listed as "other combinations" were those that could not be reliably determined (posterior P < 0.95). (**F**) The *CLEC7A* "AG/AG" haplotype associates with severity of disease as indicated by patients' earlier progression to colectomy. Haplotypes were tested for association with time to surgery by fitting the MRUC to non-MRUC ratio and time to surgery with a Cox proportional hazards model.

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drug (fig. S3). Fluconazole treatment during colitis led to reduced weight loss (Fig. 4A), and milder histological disease characteristics (Fig. 4B), specifically in *Clec7a*$^{-/-}$ mice. We similarly observed decreased T_H1 and T_H17 responses (Fig. 4, C and D, and fig. S21, A and B) and decreased production of inflammatory cytokines (fig. S21, C and D). Taken together, these results further support the conclusion that an inability to control fungi in the gut leads to more severe colitis in Dectin-1 knockout mice.

Having established a role for Dectin-1 in fungal control during colitis in mice, we next explored whether there is an association between inflammatory bowel disease (IBD) and genetic variation of the human Dectin-1 gene (*CLEC7A*). Because the mouse model suggested that Dectin-1 is involved in the severity of colonic disease, we focused our human studies on ulcerative colitis (UC), a disease of the colon, and in particular on severe UC. Up to 30% of patients with UC require colectomy, usually for severe disease that will not respond to medical therapy, including systemic corticosteroids, cyclosporine, and biological therapies [that is, medically refractory UC (MRUC)]. We compared *CLEC7A* alleles in an MRUC group with those from a group of patients with UC who had not required colectomy (non-MRUC) (*25*). We identified an association of *CLEC7A* single-nucleotide polymorphism rs2078178 in patients with MRUC (logistic regression, $P = 0.007$). Notably, a two-marker haplotype, rs2078178 to rs16910631, was more strongly associated with MRUC (AG haplotype; logistic regression, $P = 0.00013$; and Fisher's test, $P = 0.0005$) (Fig. 4E and fig. S22 and table S1), a shorter time to surgery, and thus with a more severe UC (Fig. 4F). Compared with healthy controls, the haplotype is strongly associated with MRUC and not with non-MRUC, further consistent with the idea that the haplotype is associated with severe disease (table S2). *CLEC7A* has not been identified in any genome-wide association study yet as an IBD susceptibility gene. Unlike susceptibility genes that predispose to disease, severity gene variants aggravate disease that is initially established through other mechanisms. The *CLEC7A* risk haplotype we report here fits the latter situation and agrees with our observation that *Clec7a*$^{-/-}$ mice do not develop spontaneous colitis. These findings suggest more in-depth studies on the role of the *CLEC7A* gene and pathway on the natural history of UC and will require further validation in independent cohorts.

A deeper understanding of the mechanisms by which fungi stimulate inflammatory immune responses in the gut may lead to better therapies for IBD and may be especially beneficial to patients with particularly severe forms of UC carrying the risk haplotype of the gene for Dectin-1. Overall, the idea that fungi are present in the gut and that they interact strongly with the immune system will fundamentally alter how we think about the gut microflora and inflammatory bowel diseases.

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Supplementary Materials

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Tables S1 and S2
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Chemokine Gene Silencing in Decidual Stromal Cells Limits T Cell Access to the Maternal-Fetal Interface

Patrice Nancy,[1] Elisa Tagliani,[1] Chin-Siean Tay,[1] Patrik Asp,[2]* David E. Levy,[1,2] Adrian Erlebacher[1,2]†

The chemokine-mediated recruitment of effector T cells to sites of inflammation is a central feature of the immune response. The extent to which chemokine expression levels are limited by the intrinsic developmental characteristics of a tissue has remained unexplored. We show in mice that effector T cells cannot accumulate within the decidua, the specialized stromal tissue encapsulating the fetus and placenta. Impaired accumulation was in part attributable to the epigenetic silencing of key T cell–attracting inflammatory chemokine genes in decidual stromal cells, as evidenced by promoter accrual of repressive histone marks. These findings give insight into mechanisms of fetomaternal immune tolerance, as well as reveal the epigenetic modification of tissue stromal cells as a modality for limiting effector T cell trafficking.

Besides being essential for reproductive success, the ability of the allogeneic fetus and placenta to avoid rejection by the maternal immune system during pregnancy (i.e., fetomaternal tolerance) has served as a paradigm for the study of organ-specific immune tolerance (*1*). Recent work on this problem has made use of a mouse mating system in which wild-type females are crossed with males hemizygous for the Act-mOVA transgene (*2*) to generate concepti expressing a transmembrane form of the model antigen chicken egg ovalbumin (OVA) from the ubiquitously active β-actin promoter (*3*, *4*). As early as embryonic day 7.5 (E7.5), OVA is expressed at high levels by trophoblasts directly contacting the uterus (i.e., at the maternal/fetal interface) (*3*), thus exposing maternal tissue to a surrogate fetal/placental antigen that should in principle allow for T cell priming and render the conceptus susceptible to attack by antigen-specific cytotoxic T lymphocytes (CTLs).

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Interactions Between Commensal Fungi and the C-Type Lectin Receptor Dectin-1 Influence Colitis

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The Mycobiome

In the past few years, much attention has been given to the trillions of bacterial inhabitants in our guts and the myriad of ways in which they influence our overall health. But what about fungi? **Iliev *et al.*** (p. 1314) now report that mice and humans, along with several other mammals, contain a resident intestinal population of fungi. Deletion of Dectin-1, which acts as a major innate immune sensor for fungi, led to enhanced susceptibility and worse pathology in a chemically induced model of colitis in mice. A polymorphism in the gene that encodes Dectin-1 has been observed in patients with ulcerative colitis, which hints that, besides the traditional bacterial microbiome, alterations in the "mycobiome" may also play a role in health and disease.

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