but the precise biochemical functions of the ATPase in the evolutionarily divergent apicomplexa remain to be established.

As transmembrane proteins, the hybrid GCs could be receptors or sensors that link extracellular signals to cellular responses in the parasite. It is tempting to speculate that the ATPase domains play a role in transducing such signals. Whether ookinete gliding can be triggered or directed toward the mosquito midgut epithelium by extracellular signals is unknown. However, tachyzoites egress from host cells in response to a low potassium environment that occurs upon host-cell rupture (Moudy et al., 2001), and *Plasmodium* gametocytes get activated by the mosquito environment through a cGMP/PKG dependent pathway (Brochet et al., 2014). If and how GCs transduce these signals is now the next question.

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Exploring the Gut Fungi-Lung Allergy Axis

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Gut fungal dysbiosis exacerbates colitis and lung allergy. In recent studies published in *Science* (Leonardi et al., 2018) and *Cell Host & Microbe* (Li et al., 2018), gut-resident CX_3CR1^+ mononuclear phagocytes were found to mediate crosstalk between intestinal fungi and systemic immunity along the lung-gut axis during homeostasis and inflammation.

Most animals, including humans and rodents, live symbiotically with vast arrays of microorganisms. The gut is a major organ in which microorganisms reside; it contains trillions of microbes, including bacteria, viruses, and fungi. An imbalance in gut microbial composition—dysbiosis—can be caused by many factors, including host genetics, lifestyle, exposure to microorganisms, and medical treatment. Gut dysbiosis has been associated not only with intestinal inflammation but also with many diseases distant from the gut, such as atopic dermatitis, allergy, cancer, obesity, and diabetes (Honda and Littman, 2016).

Fungal dysbiosis can be caused by at least two factors, namely antibiotic or antimycotic treatment. Antibiotic treatment affects not only gut bacterial composition but also sometimes fungal composition (Noverr et al., 2004; Kim et al., 2014), perhaps due to the elimination of bacterial species that promote resistance to fungal growth in the intestine. In contrast, ironically, antimycotic therapy can induce fungal dysbiosis by promoting the overgrowth of drug-resistant filamentous fungi. For example, prolonged oral treatment of mice with the antifungal drug fluconazole suppresses the growth of *Candida* spp. but increases the abundance of *Aspergillus*, *Wallemia*, and *Epicoccum* in the intestine (Wheeler et al., 2016). Interestingly, fluconazole treatment can result in the overgrowth of drug-resistant gut fungi for several weeks after the cessation of treatment (Li et al., 2018). Although gut fungal populations are minor components of the gut microbiota, fungal dysbiosis can lead to the development of intestinal inflammatory diseases such as Crohn's disease or ulcerative colitis, alcoholic liver disease, or allergic inflammation in the lung (Wheeler et al., 2016). In this regard, an elegant study by Li et al. (2018) in this issue provides formal evidence that gut fungal

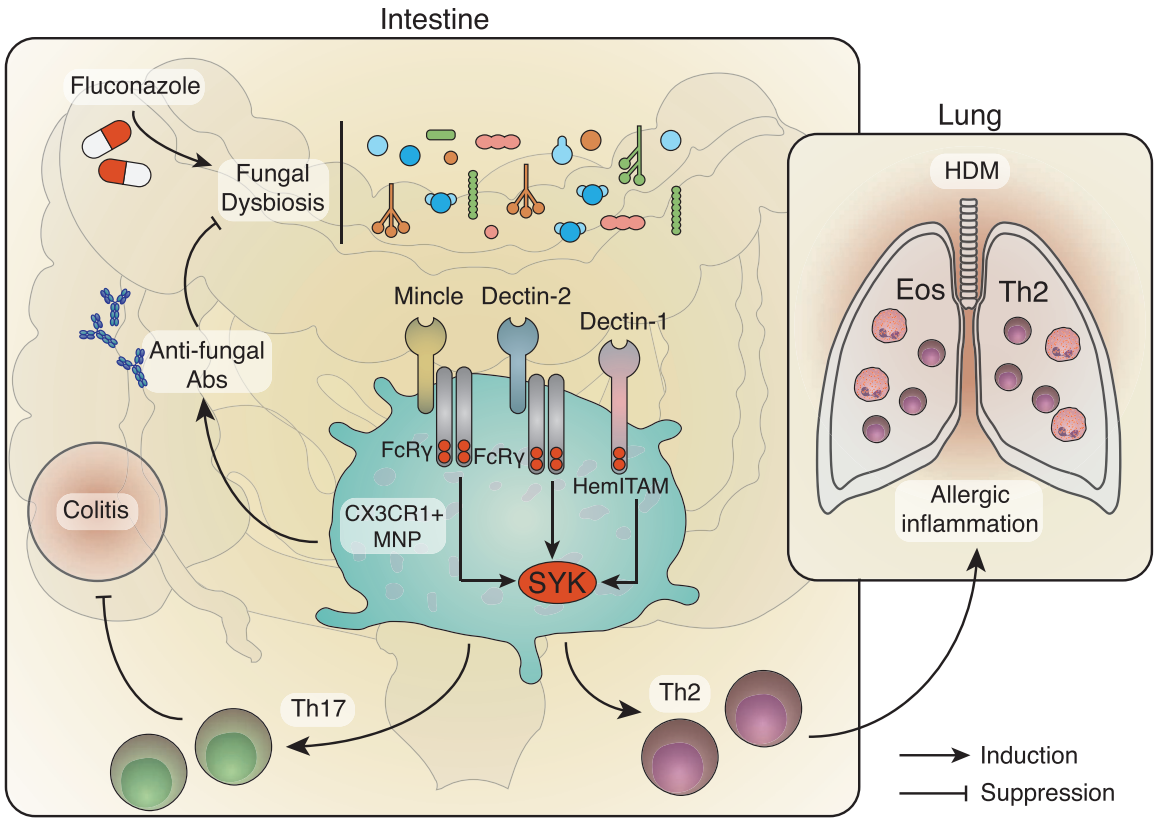

Figure 1. The Gut CX3CR1+ Mononuclear Phagocytes as Key Links between Gut Fungi and Inflammation in the Lung and Intestine
Fluconazole-induced dysbiotic fungal community directly stimulates CX3CR1+ MNPs via the fungal C-type lectin receptors, resulting in the Th17 and Th2 responses in the intestine. These responses in turn lead to suppression of intestinal inflammation and exacerbation of allergic airway inflammation, respectively.

dysbiosis activates the gut fungi-lung allergy axis. They used gnotobiotic mice colonized with altered Schaedler flora: a minimal bacterial community consisting of a defined set of functionally diverse anaerobic and aerobic bacteria, but lacking fungi. Fluconazole treatment of these mice had no effect on house-dust-mite (HDM)-induced allergic lung inflammation. However, HDM-induced lung inflammation was exacerbated by oral supplementation of the fluconazole treatment with a dysbiotic fungal community, including *Aspergillus amstelodami*, *Epicoccum nigrum*, and *Wallemia sebi* (Li et al., 2018), which grow in response to fluconazole treatment in specific-pathogen-free mice, as described above (Wheeler et al., 2016). Fluconazole-induced growth of dysbiotic fungi in the gut was thus sufficient to exacerbate lung allergy. Because fluconazole is often used to treat immunocompromised patients or patients with mucosal or vulvovaginal candidiasis, careful attention should be paid to fungal dysbiosis induced by this drug. However, how fungal dysbiosis induces inflammation of both the intestine and organs distant from it remains poorly understood.

In an effort to determine how gut fungi modulate host immunity and inflammation, Leonardi et al. (2018) postulated that a certain subset of immune cells in the intestinal lamina propria might interact with gut fungi. They found that, among the myeloid cells in the intestine, only mononuclear phagocytes (MNPs) expressing the fractalkine receptor CX_3CR1 upregulated the expression of CD40 and CD86 costimulatory molecules when the mouse gut was colonized with the opportunistic human commensal *Candida albicans*. CX_3CR1^+ MNPs expressed the fungal C-type lectin receptors (CLRs) Dectin-1 (*Clec7a*), Dectin-2 (*Clec6a*), and Mincle (*Clec4e*) and were able to phagocytose *Candida albicans* in the intestine. Dectin-1 contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic tail. Dectin-2 and Mincle associate with the ITAM-bearing adaptor protein Fc receptor-γ chain (FcRγ) through a positively charged amino acid residue in their transmembrane regions. Because the ITAM is phosphorylated and mediates an activating signal via spleen tyrosine kinase (Syk) in myeloid cells, the response of CX_3CR1^+ MNPs to fungi is Syk dependent (Leonardi et al., 2018). Genetic ablation of CX_3CR1^+ MNPs in mice leads to gut fungal dysbiosis, and, unlike in wild-type mice, a dramatic decrease in the numbers of Th17 cells in the colon and mesenteric lymph nodes and severe dextran sulfate sodium-induced colitis; there is also a defect in antifungal antibody production (Leonardi et al., 2018). A recent study demonstrated that IL-17F, but not IL-17A, is involved in the development of inflammatory bowel diseases (Tang et al., 2018). IL-17A instead targets epithelial cells in the intestine and promotes the activation of regulatory pathways that protect the gastrointestinal tract (Lee et al., 2015), suggesting that CX_3CR1^+ MNPs are involved in the activation or differentiation of Th17 cells producing IL-17A, but

not IL-17F. Moreover, CX_3CR1^+ MNPs produce IL-23, which supports group 3 innate lymphoid cells (ILC3s) to produce IL-22, thus protecting epithelial cells from microbiota-induced colitis (Longman et al., 2014). Interestingly, Leonardi et al. (2018) found that CX_3CR1^+ polymorphisms are associated with impaired antifungal responses in patients with Crohn's disease, who are unable to produce antibodies against multiple fungal species. Leonardi et al. (2018) concluded that CX_3CR1^+ MNPs play an important role in innate and adaptive immune responses to fungi in a Syk-dependent manner and mediate the interaction between gut fungi and host intestinal homeostasis and inflammation (Figure 1).

CX_3CR1^+ MNPs are abundant not only in the intestine but also in the lung. To address the question of whether intestinal CX_3CR1^+ MNPs, which interact directly with gut fungi, are also involved in inflammatory diseases in organs distant from the intestine, such as the lung, Li et al. (2018) generated mice in which CX_3CR1^+ MNPs were specifically deleted from the intestine, but not from the lung. Compared with control mice, after fluconazole treatment, these mice showed a dramatic amelioration of HDM-induced allergic airway inflammation and a reduction in Th2 responses (Figure 1). Interestingly, Syk inhibition in intestinal CX_3CR1^+ MNPs suppressed HDM-induced lung inflammation and decreased the numbers of Th2 cells in both the intestine and lung of these fluconazole-treated mice. Because a positive correlation between IL-17A production and asthma severity has been established (Chesné et al., 2014), it is possible that Th2 cytokines and IL-17A—the production of both of which is increased in association with CX_3CR1^+ MNP activity in response to gut fungal dysbiosis—cooperate in the exacerbation of allergic airway inflammation. Fungi produce prostaglandins that promote M2 macrophage polarization in the lung, thus exacerbating allergic airway inflammation (Kim et al., 2014). Therefore, there are two gut-fungus-associated pathways that lead to allergic airway inflammation: the production of metabolites such as prostaglandin derived from the fungi themselves, and the production of immune cells such as CX_3CR1^+ MNPs that directly recognize fungi in the intestine.

Although Iliev and colleagues have demonstrated that gut CX_3CR1^+ MNPs play both a protective role in gut-fungus-associated colitis and a pathogenic role in allergic airway inflammation (Leonardi et al., 2018; Li et al., 2018) (Figure 1), several important issues remain unclear. First, although fluconazole treatment enhances the growth of *A. amstelodami*, *E. nigrum*, and *W. sebi* (Leonardi et al., 2018), it would be interesting to determine which fungus (or fungi) specifically stimulates CX_3CR1^+ MNPs to activate either Th17 cells or Th2 cells, or both, and to elucidate how CX_3CR1^+ MNPs set the pathway leading to adaptive immunity through the Th17 response or that through the Th2 response. Second, although gut CX_3CR1^+ MNPs are involved in an increase in Th2 cell numbers in both the lung and intestine in response to HDM in mice treated with fluconazole (Li et al., 2018), it is unclear how the intestinal Th2 cells are involved in the increase in numbers of lung Th2 cells. In other words, are the origins of both intestinal and lung Th2 cells the same (i.e., do the intestinal Th2 cells migrate into the lung) and, if so, what is the antigen specifically recognized by the Th2 cells? Alternatively, it is possible that the increase in the number of intestinal Th2 cells via the action of CX_3CR1^+ MNPs in response to gut fungal dysbiosis promotes the activation of HDM-induced lung Th2 cells via cytokines such as IL-4. Elucidation of these issues would definitively help further our understanding of the pathophysiology of inflammatory diseases associated with gut fungal dysbiosis and to develop novel therapeutic approaches to these conditions.

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