HHS Public Access

Author manuscript

Cell Host Microbe. Author manuscript; available in PMC 2021 May 10.

Published in final edited form as:

Cell Host Microbe. 2021 March 10; 29(3): 311–312. doi:10.1016/j.chom.2021.02.014.

Local Farming of Gut Fungi Protects Against Dangerous Imports

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SUMMARY:

Candida albicans is viewed as a harmless commensal in health and a dangerous parasite in disease. Recently in *Cell*, Doron et al (2021) reveal that *C. albicans* in the gut additionally serves as a mutualist by provoking the immune system to generate far-reaching antibodies that defend against invasive fungal infections.

The microbiome is a rich ecosystem of bacteria, fungi and other microorganisms that live in and on humans and animals. In particular, microbial communities residing in the intestines (i.e. gut microbiota) profoundly impact human health in many – and often times unexpected – ways. When healthy, the gut microbiota supplies essential nutrients to the host, self regulates microbial growth and tempers inflammation (Kau et al., 2011). However, if gut microbiota harmony breaks down (i.e. dysbiosis) due to antibiotic usage, dietary alterations, immune suppression, etc., a multitude of diseases can arise. These maladies can include microbial translocation and invasive infection, local inflammation (e.g., colitis) and even remote inflammation like allergic asthma in the lungs (Kau et al., 2011).

Fungi comprise a much smaller proportion of the gut microbiota compared to bacteria (Arumugam et al., 2011), which may superficially explain why our understanding of the relationship of gut fungi with health and disease lags behind that of bacteria (Li et al., 2019). Notwithstanding, several pertinent features of the fungal "mycobiota" are well established. *Candida albicans* is a commensal fungus in humans (and can be seeded in mice) that thrives on most surfaces of the body, including the gut. Additionally, *C. albicans* exploits situations of dysbiosis and/or immune suppression to invade tissues and cause devasting disease (Li et al., 2019). Although T cell-mediated immunity is a widely recognized pathway for protection against invasive *Candida* infection (Bacher et al., 2019), the function of the humoral arm of the immune system is more controversial. Anti-fungal antibodies are prevalent in humans in both disease and health, thus obscuring the function of these antibodies in causing or preventing disease (Li et al., 2019). In a recent publication in *Cell*, Doron and colleagues create and utilize technology, robust animal models and human data to elucidate a detailed mechanism of how an immune cell subset recognizes and responds to *C. albicans* in the gut to "farm" antibodies that protect against invasive candidiasis (Figure 1) (Doron et al., 2021).

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Doron et al. developed a powerful strategy – termed “Multi-kingdom Antibody Profiling” – to identify fungal species in the gut that are bound by antibodies circulating in the periphery. This technique allowed the authors to elucidate several remarkable features of the gut mycobiota (Doron et al., 2021). Compared to previous metagenomic estimates of the relative proportion of fungi in the human gut at <0.5% (Arumugam et al., 2011), Doron and colleagues calculated a much higher relative abundance of fungi at ~2%. The authors also determined that most of these fungi were bound by IgA and/or IgG antibodies. IgA antibodies are generally restricted to mucosal surfaces, particularly in the gut; whereas, IgG antibodies are largely found in systemic circulation. The authors noted that ~20% of fungi in the human gut could bind systemic IgG antibody, and the fungi bound by these systemic antibodies were primarily *C. albicans*. Given the high potential for systemic disease caused by *C. albicans*, this was an intriguing discovery that the authors smartly pursued to unravel an important mechanism of immunity to systemic fungal infection.

Using animal models, which allow for tight control over host genetics and microbiota composition, the authors investigated the therapeutic potential of systemic IgG to protect against invasive candidiasis (Doron et al., 2021). Adoptive transfer of antibody-producing B cells from *C. albicans*-colonized mice into B cell deficient mice significantly extended survival and reduced fungal burden in the kidneys following lethal intravenous infection with *C. albicans*. Similarly, passive transfer of sera (containing anti-*C. albicans* IgG) from *C. albicans*-colonized mice protected recipient mice from both intravenous *C. albicans* infection, as well as lethal disease caused by immunosuppression and ensuing *C. albicans* gut translocation and invasive infection. Sera from *C. albicans*-colonized mice also prevented fungal dissemination to the brain after intravenous infection with the emerging fungal pathogen, *C. auris*, thereby indicating a capacity for cross-reactivity of anti-*C. albicans* antibodies. Importantly, all of these experimental models represent modalities of human disease: fungal bloodstream infection via catheterization, fungal gut translocation in immunosuppressed patients with cancer or transplant recipients, and nosocomial infection with *C. auris* (Brown et al., 2012). In sum, the authors firmly demonstrated that antibodies “farmed” from the mycobiota have a far-reaching impact on preventing invasive candidiasis.

Primary immunodeficiencies enlighten and guide our understanding of basic immunology. The authors leveraged this paradigm to elucidate a signaling pathway and immune cell subset involved in the production of systemic anti-*C. albicans* IgG. CARD9 is an adapter protein that connects fungal carbohydrate recognition to proinflammatory gene transcription in immune cells. Mutations in *CARD9* are strong risk factors for invasive fungal infection (Glocker et al., 2009) and *CARD9*-deficiency in mice causes gut fungal dysbiosis (Lamas et al., 2016). Thus, Doron and colleagues formulated and subsequently validated the hypothesis that *CARD9* is required for B cell priming and systemic anti-*C. albicans* IgG antibody production as a consequence of gut colonization with *C. albicans* (Doron et al., 2021). CARD9 expression was mostly restricted to phagocytes within the gut, including CX3CR1+ mononuclear phagocytes, and a missense mutation in *CX3CR1* has been previously shown to cause a deficit in systemic anti-fungal IgG in Crohn’s Disease patients (Leonardi et al., 2018). When CX3CR1+ mononuclear phagocytes were depleted, *C. albicans*-colonized mice exhibited a striking defect in anti-*Candida* IgG. A similar result was observed when *SYK*, a kinase that activates CARD9, was conditionally deleted in

CX3CR1+ mononuclear phagocytes. Finally, and perhaps most impressively, the authors identified several *CARD9* polymorphisms in humans that correlated with invasive candidiasis and defects in serum anti-*C. albicans* IgG. Collectively, the authors mapped a detailed immunologic circuit, further supported by evidence in humans. CX3CR1+ mononuclear phagocytes detect gut fungi via SYK and CARD9. This information is then relayed indirectly to splenic B cells, leading to high affinity anti-*C. albicans* antibody production, and their subsequent release into the periphery.

There are a few major take home messages from this study (Figure 1) (Doron et al., 2021). First, antibodies specific for gut fungi circulate throughout the body, and these antibodies potently protect against invasive fungal infection. Additionally, a mononuclear phagocyte subset recognizes the gut fungi via SYK and CARD9 which leads to the production of these widely disseminated fungal antibodies. However, like many exceptional studies, the work by Doron et al. generates more questions than it provides answers. How early in life do anti-*C. albicans* antibodies appear in circulation, and do they wane with age? What is the connection between CX3CR1+ mononuclear phagocytes at the gut mucosa and B cell priming/affinity maturation in the spleen? Does the SYK/CARD9 axis activate the inflammasome in CX3CR1+ mononuclear phagocytes to promote gut health as has been previously reported with more broadly defined macrophages (Malik et al., 2018)? Do other gut fungi function as mutualists in similar ways as *C. albicans*? Is the farming of gut fungi for antibodies that protect against the threat of systemic invasion by loosely related fungi an example of “anticipatory immunity”? A multitude of other questions will undoubtedly follow.

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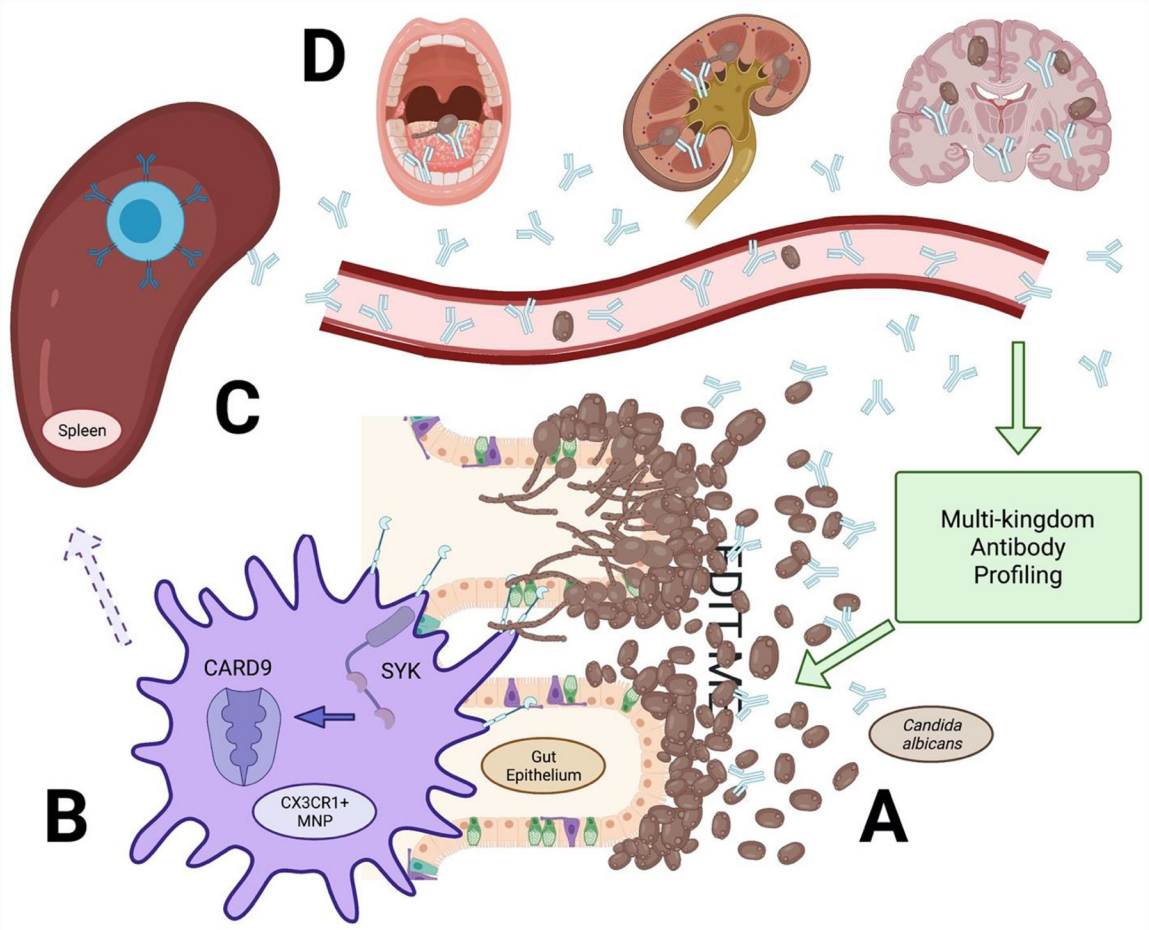

FIGURE 1.

Candida albicans is "Farmed" by Gut-resident Mononuclear Phagocytes Which Leads to Systemic Release of Protective Anti-fungal Antibodies. **(A)** *C. albicans* colonize the gut mucosa. **(B)** CX3CR1+ mononuclear phagocytes recognize gut fungi and signal via SYK and CARD9 to (**C)** promote the production of anti-*C. albicans* antibodies in the spleen. **(D)** anti-C. albicans antibodies enter blood circulation and defend against invasive candidiasis.