C-type lectin receptors as potential targets for the treatment of gastrointestinal diseases related to fungal infection

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Many microorganisms reside in the gastrointestinal tract and the dysbiosis of microorganisms can affect our health. Fungi have a relatively low level of presence (about 0.1% of the total microorganisms) compared with bacteria, which makes it easier to underestimate their potential threat to health. However, fungal infections indeed participate in the onset and progression of many intestinal diseases, so they are crucially affecting our health [1, 2].

Recently, Li et al. described that C-type lectin receptors (CLRs) on myeloid cells, including Dectin-1, Dectin-2, Dectin-3, and Mincle, play an important role in the immune function induced by fungal pathogens of the intestinal microbiota [3]. After being recognized by CLRs expressed on phagocytic cells, the invasive microorganisms are internalized through the process of phagocytosis. Particularly, this causes most CLRs to interact with spleen tyrosine kinase (Syk), enabling downstream signals to activate NF-κB via CARD9-Bcl10-MALT1 complex. This signaling leads to the secretion of pro-inflammatory cytokines and initiates the differentiation of naïve T cells into different T-helper-cell lineages, which are crucial to antifungal immunity (Figure 1). The entire process eventually induces both innate and adaptive immunity, and plays an important role in gastrointestinal antifungal immunity [3, 4].

CLRs alter the composition of gut microbiota, which plays an important role in gastrointestinal illness. Dectin-1 or -3-deficient mice are susceptible to dextran sodium sulfate (DSS)-induced colitis. The specific fungal burden of Candida tropicalis is markedly increased in the gut after DSS treatment in mice lacking Dectin-1 or -3. Moreover, colitis symptoms are much more severe in mice lacking Dectin-1 or -3 supplemented with C. tropicalis compared with control mice. In contrast, C. tropicalis supplementation does not aggravate colitis in wild-type mice [5, 6].

Chronic inflammation plays an important role in the development of colorectal cancer (CRC). Patients with inflammatory bowel disease have a higher risk of developing CRC. Dectin-1 and -3 are implicated to have protective roles against pathogenic fungi in DSS-induced colitis and the functional role of fungi in the development of CRC has been recently characterized. Multiple pattern-recognition receptors (PPRs) of the CLRs require caspase recruitment domain-containing protein 9 (CARD9) for the activation of innate immunity. As such, CARD9 links the detection of fungi to the activation of the NF-κB pathway. Wang et al. demonstrated the impact of CARD9 in the development of colitis-induced colon cancer, where treatment of AOM-DSS (azoxymethane and dextran sodium sulfate) in CARD9 –/– mice resulted in increased tumor burden when compared with wild-type mice. Notably, CARD9 –/– mice macrophages have impaired fungicidal functions, which in turn leads to increased variation in the overall composition of the intestinal mycobiota, with a notable increase in C. tropicalis [7]. These data suggest that fungal infection has a role in colon carcinogenesis.

Targeting the link between chronic inflammation and fungal sensing may provide a new therapeutic strategy to prevent gastrointestinal diseases, including cancer. It has been shown that Dectin-3-deficient mice are very susceptible to DSS-induced colitis when compared with wild-type mice. Antifungal therapy using fluconazole—a drug for treating fungal infections—is effective in treating colitis in Dectin-3-defective mice [6]. Also, another study demonstrated that antifungal treatment...
ameliorates colitis-associated cancer in CARD9 \(-/-\) mice [7].

JNK1 can negatively control antifungal innate immunity by suppressing CD23 expression. Treatment of JNK inhibitors demonstrates potent antifungal effects in *C. albicans*-infected mouse and human cells, suggesting that JNK1 is a potential therapeutic target for treating fungal infection [8].

Further research is required to gain a deeper understanding of the role of the CLRs in gastrointestinal diseases, including cancers. Early steps in employing the interaction between commensal fungi and intestinal immune responses for treatment design have been established. While we are still at the beginning of understanding of CLR-signaling pathways, future studies exploring detailed molecular mechanisms will help to develop more approaches targeting CLR-signaling pathways. In conclusion, further studies are warranted to identify how the functions of the fungal community (mycobiome) are involved in gastrointestinal diseases and to develop strategies to strengthen the defense when treating gastrointestinal diseases.

Conflicts of interest
The authors declare no competing financial interests.

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Figure 1. Activation of CLRs induced by the binding of gut fungi activates Syk/CARD9/NF-\(\kappa\)B pathways to exert antifungal activity. CLRs, C-type lectin receptors; Syk, spleen tyrosine kinase; IL-6, Interleukin 6; NF-\(\kappa\)B, nuclear factor kappa-B; CARD9, caspase recruitment domain-containing protein 9.