Although the impact of intestinal bacteria and their derivatives in the regulation of colon physiology and pathology had been considerably explored, less is known on the role of intestinal fungi. Fungi form the “mycobiome”, which is particularly abundant in the colon and has been associated with distinct colon inflammatory pathologies, including inflammatory bowel diseases (IBD) and colorectal cancer. We recently uncovered the key role of macrophages, immune sentinels from the myeloid compartment, in regulating the interactions between fungi and colonic epithelial cells. For this, macrophages use “balloon-like-protrusions” (BLPs) inserted in between epithelial cells, which perform a quality check of absorbed fluids and limit the absorption of toxic fungi metabolites accordingly. In the absence of macrophages or their protrusions, colonic epithelial cells die and intestinal barrier integrity is lost.

Here, we postulate that (i) through their dialog with fungi and epithelial cells, BLP+ macrophages set the inflammatory status of the colon, and (ii) failure in this regulatory process might lead to impairment of local immune responses and establishment of colon pathology. We propose a project articulated in four aims to test these hypotheses. In Aims 1 and 2, we will identify the molecular players and mechanisms involved in the fungi-dependent dialog between BLP+ macrophages and epithelial cells. In Aims 3 and 4, we will build up on this analysis to evaluate how this dialog regulates the inflammatory status of the colon, thereby defining the efficiency of local immune responses and the susceptibility to IBD and colon cancer.

This study will provide the first comprehensive view on how macrophages regulate the interactions between epithelial cells and the mycobiome at the molecular, cellular and tissue scales, and how dis-regulation of these interactions impacts colon physiology and pathology.
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