Saccharomyces boulardii as a Treatment for Colonic-inflammatory Conditions such as Chemotherapeutic-induced Mucositis and Colorectal Cancer

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Abstract

Chemotherapeutic-induced mucositis (CIM) is a prevalent and debilitating side effect of cancer treatment, characterized by inflammation and ulceration of the gastrointestinal (GI) tract. Current treatments focus on controlling symptoms; however, recent research has focused on using probiotics such as *Saccharomyces boulardii (S. boulardii)* as a potential treatment for CIM given its ability to restore gut dysbiosis, facilitate cell growth, and strengthen the mucin barrier. CIM shares pathophysiological features such as gut dysbiosis and intestinal inflammation with inflammatory bowel disease (IBD) as well. Patients with IBD are at increased risk for developing colorectal cancer (CRC), highlighting the importance of understanding the relationship between inflammation and tumorigenesis in the GI tract. Probiotics such as S. boulardii have shown promise in alleviating the symptoms of IBD and reducing CRC risk; however, S. boulardii does not stably colonize and is not retained well in the GI tract thereby necessitating daily and high dosing. Our team has developed an engineered *S. boulardii* designed to attach to the fibronectin moieties that are highly expressed on ulcerated tissue in the GI tract and secrete nanobodies against pro-inflammatory TNFα. To validate the CIM model, female FVB mice were intraperitoneally injected with irinotecan or saline three times a week for two weeks. The measured outcomes included body mass, Bristol Stool scores, fecal occult blood, and fecal lipocalin-2 concentrations. To validate the AOM/Il10-/- model for colitis-associated cancer, germ-free 129SvEv Il10-/- mice were colonized with fecal microbiota transplant to begin inducing inflammation and then intraperitoneally injected once weekly for six weeks with AOM to induce tumorigenesis. As a probiotic treatment, mice received oral gavages of engineered *S. boulardii* once or twice weekly, unmodified *S. boulardii* twice weekly, or PBS once weekly. The measured outcomes included body mass, macroscopic tumor counts and sizes, histological neoplasia scores to quantify the severity of neoplasia and tumor invasion, and histologic inflammation scores. For CIM model validation, mice injected with irinotecan did not exhibit significant weight loss, have higher Bristol Stool scores, test positive for fecal occult blood, or have significantly higher concentrations of fecal lipocalin-2 than irinotecan-untreated mice. our inability to validate the model prevented us from evaluating the efficacy of *S. boulardii* in treating CIM. We were able to successfully run the AOM/Il10-/- model for colitis-associated cancer, where both inflammation and invasive tumors (adenocarcinoma) were successfully induced. In this model, *S. boulardii* decreased tumor multiplicity and tumor load in a dose-dependent manner regardless of engineered properties. In addition, there was no significant difference between unmodified and engineered *S. boulardii* in terms of colonization efficiency. These findings suggest that *S. boulardii* exhibits anti-cancer activity and should also be evaluated for ameliorating mucositis associated with other anti-cancer regimens like chemotherapy following model validation. Our findings also suggest that engineered *S. boulardii* may also hold promise as a treatment for inflammation-associated CRC, but we must identify a targeting ligand to improve colonization.