

The role of fungi in irritable bowel syndrome (IBS): new insights in human disease development

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INTRODUCTION

Irritable bowel syndrome (IBS) is a major cause of gastro-intestinal discomfort with visceral hypersensitivity as one of the characteristic features. Bacterial dysbiosis might be involved in the activation of nociceptive sensory pathways, but the role of the mycobiome (the fungal microbiome) is hardly studied. We analyzed intestinal mycobiomes of patients with IBS and of a rat model of visceral hypersensitivity. Also therapeutic interventions have been studied.

METHODS

Neonatal maternal separation in Long Evans rats predisposes for stress-induced visceral hypersensitivity at adult age. This model mimics early adverse life events shown to be associated with increased risks of IBS later in life.

DNA was isolated from human and rat fecal samples. Barcoded fungal internal transcribed spacer regions (ITS) amplicons were generated and analyzed by MiSeq sequencing. Sequence assignment was based on comparison with the Unite database.

RESULTS

Mycobiome composition of IBS patients (both hyper and normosensitive) was clearly different from healthy controls (Figure 1).

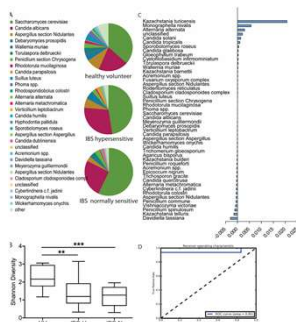


Figure 1. Differences in mycobiome between healthy volunteers (HV), hypersensitive irritable bowel syndrome (IBS-H) and normally sensitive (IBS-N) patients

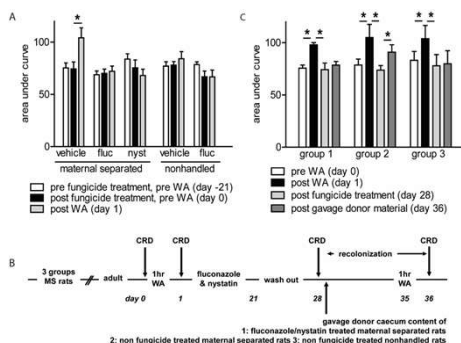


Figure 2. Fungi are important for water avoidance (WA)-induced visceral hypersensitivity of maternal separated (MS) rats.

RESULTS

Water avoidance testing showed different behavior between maternally separated and non-handled rats. Treating maternally separated rats with the antifungal fluconazole or nystatin restored behavior to the non-handled situation (Figure 2). DNA analysis of fecal samples from the different groups also showed differences in mycobiome composition (Figure 3).

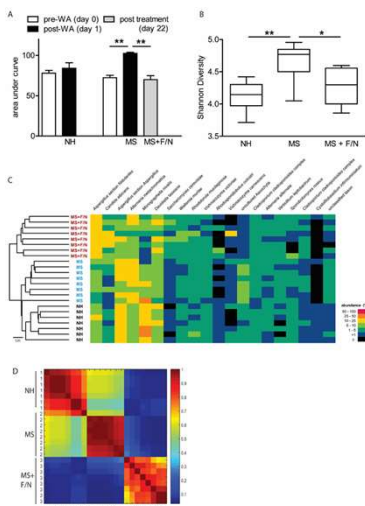


Figure 3. Differences in mycobiome between nonhandled (NH) and maternal separated (MS) rats.

The intestinal mycobiome is not dominated by a single species, but harbors a complex ecosystem comparable to the intestinal microbiome, with different abundances of specific fungi in the different rat groups (Figure 4).

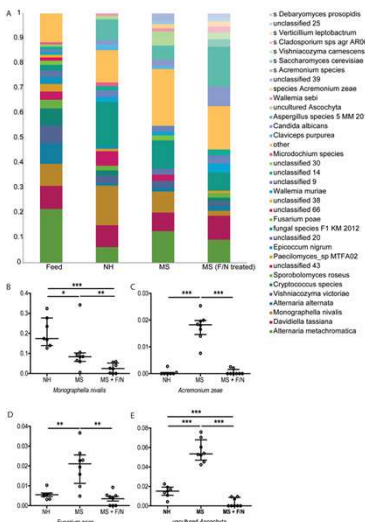


Figure 4. Mycobiome composition of rat feces and feed, and differences between selected fungal species

RESULTS

The connection between fungi and the host (pain) response involves the Dectin1/Syk pathway and amongst others mast cell degranulation (Figure 5). A proposed mechanism is shown in Figure 6.

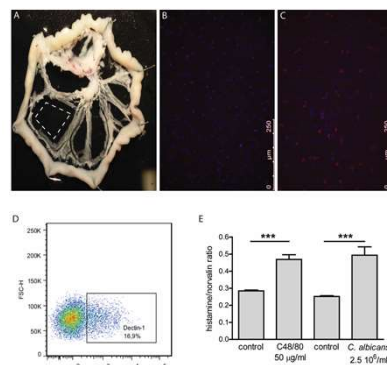


Figure 5. Fungal induced mast cell degranulation.

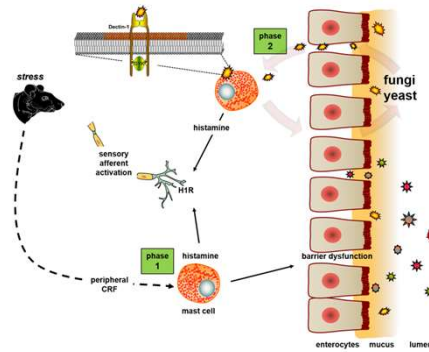


Figure 6. Proposed mechanism of the role of fungi in stress-induced visceral hypersensitivity in maternal separated rats.

CONCLUSIONS

> Differences in mycobiome composition were shown between IBS patients and healthy controls reminiscent to the shifts found in the rat model.

> In a rat model for visceral hypersensitivity also differences in mycobiome composition could be shown which were related to the pain phenotype.

> Causal relationship could be shown based on treatment with antifungals and fecal transfer between hypersensitive and normal rats.

> We are currently investigating a broader role of fungi in chronic inflammatory diseases in humans.

REFERENCES

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Botschuijver et al (2018) Neurogastroenterology Motil DOI: 10.1111/nmo.13299