

TAVOLA ROTONDA

Modulazione del microbiota nella patologia umana

Micobioma



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Società Italiana di Neuro-Gastro-Enterologia e Motilità

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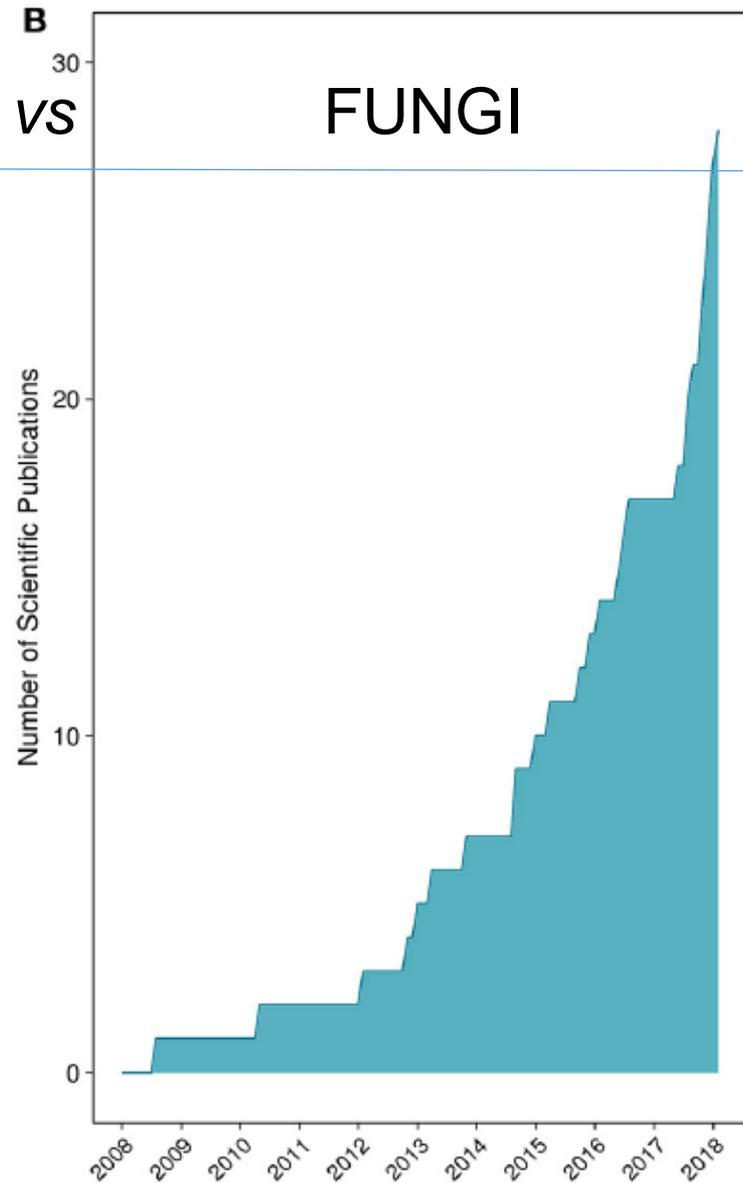
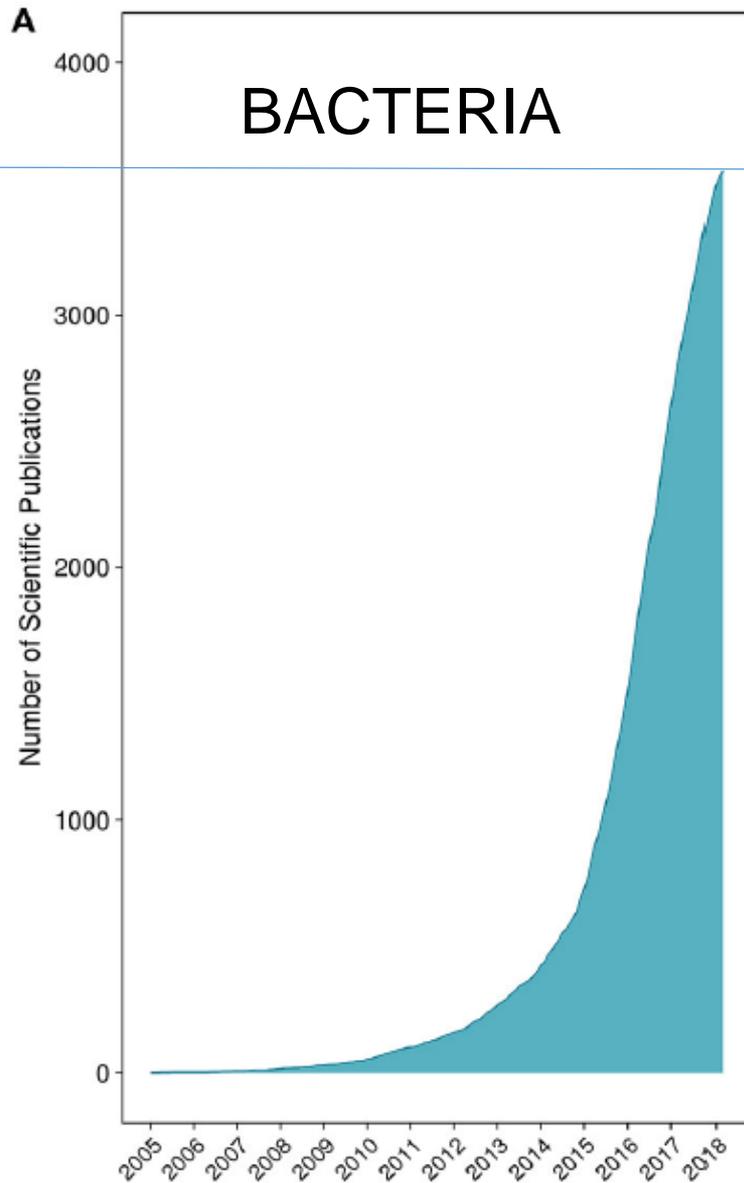
CONGRESSO
NAZIONALE
SINGEM



The intestinal mycobiome

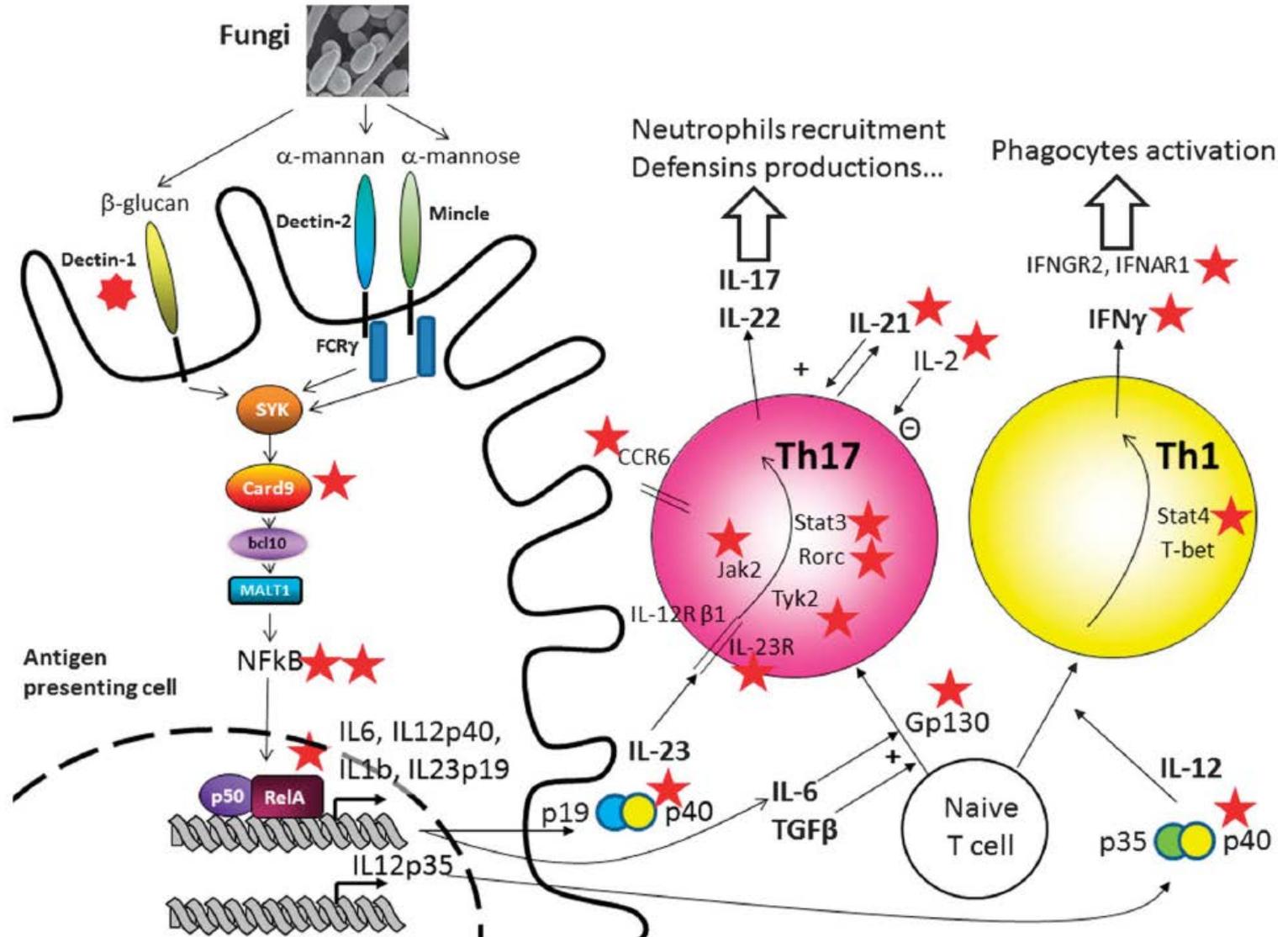
- ✓ Fungi represent a relative small amount of the whole intestinal microbiota, accounting for about 0.1% of the total load of microorganisms
- ✓ The majority of fungi colonizing the intestinal tract include the *Candida* (i.e. *C. albicans*) and *Saccharomyces* genus (i.e. *S. cerevisiae*)
- ✓ Studies support the occurrence of a competitive relationship between fungi and bacteria in the gut
- ✓ The composition of the intestinal mycobiome can be influenced by different factors, such as diet, age, sex and genetic factors, and it is much less stable over the time compared to the bacterial population

Research on gut mycobiome is only at the beginning



INTESTINAL MYCOBIOME IN IBDs

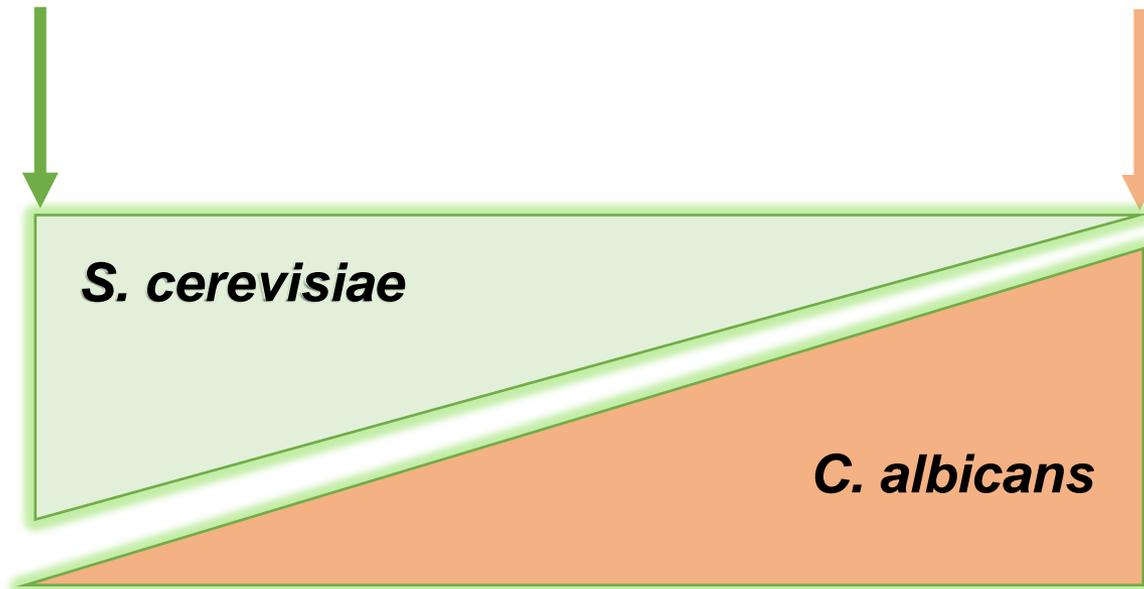
Signal transduction pathways activated by the immune response towards fungal antigens: genetic polymorphisms associated to IBDs



Intestinal fungal dysbiosis is frequently observed in IBDs

Normal

INFLAMMATION



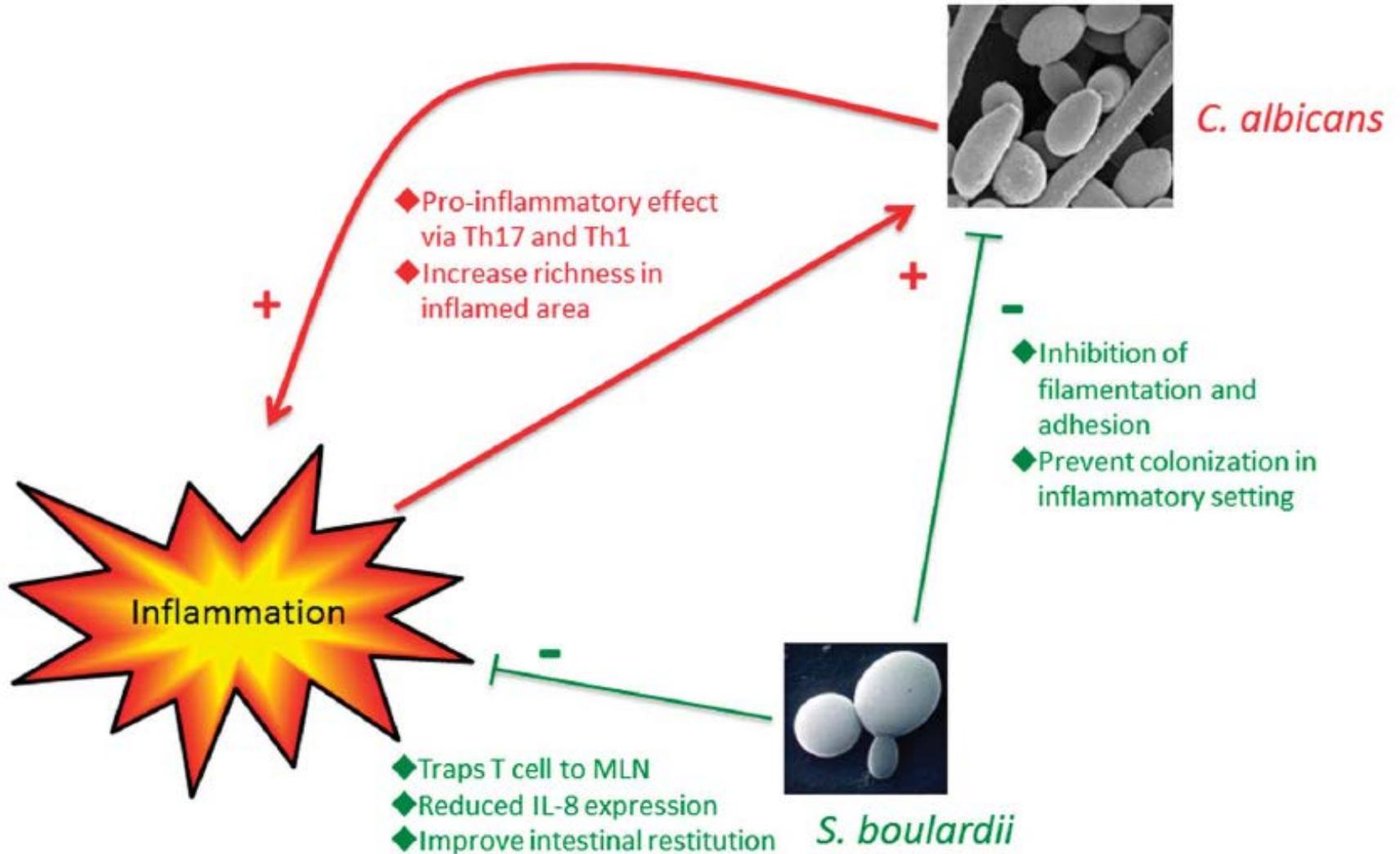
Li et al., J Clin Gastroenterol 2014, 48:513–523

Sokol et al., Gut 2017, 66:1039–1048

Liguori et al., Crohns Colitis 2015, 10:296–305

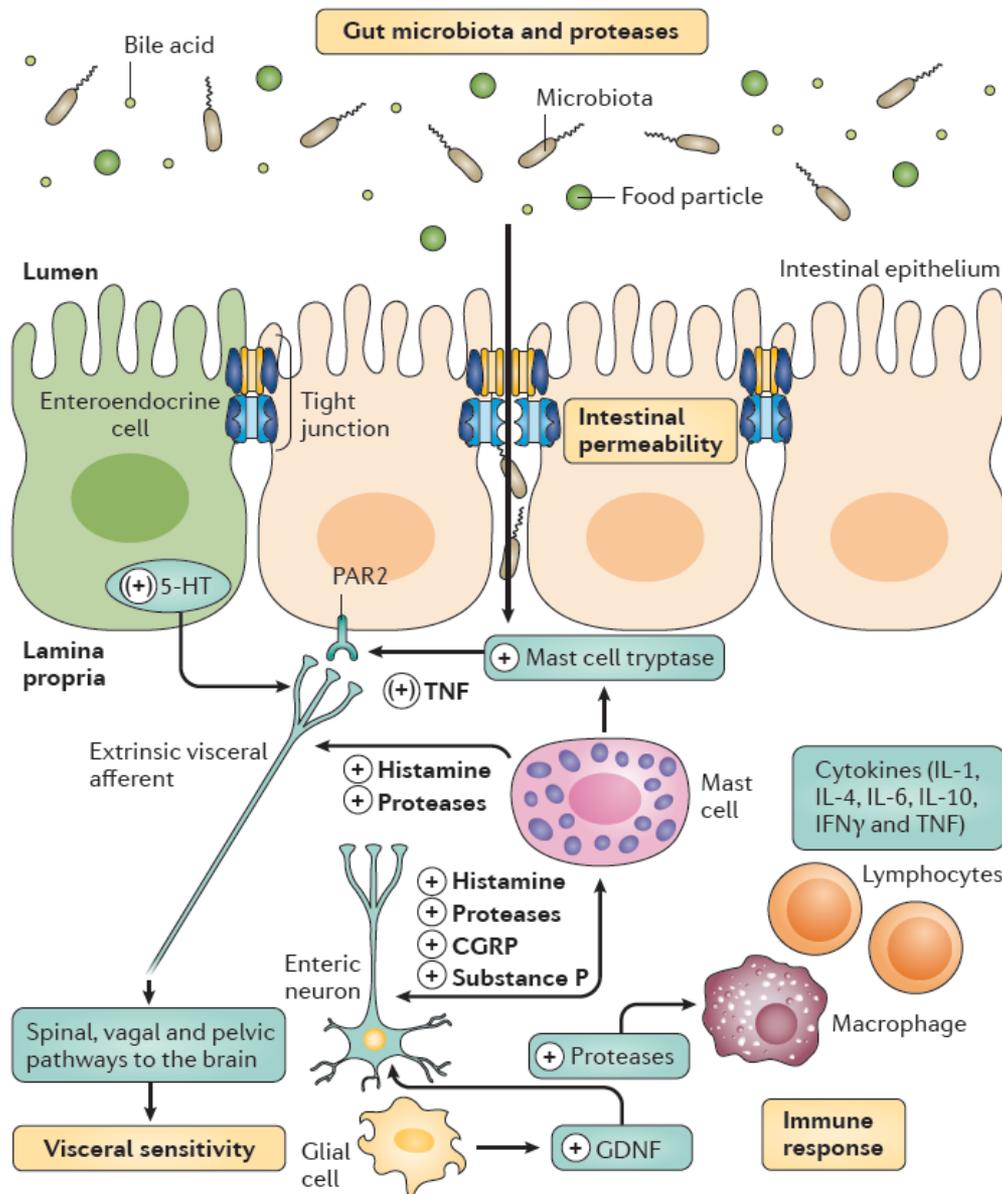
Hoarau et al., Mbio 2016, 7:e01250–e01216

Opposite actions of *C. albicans* and *S. boulardii* in the pathophysiology of IBDs



INTESTINAL MYCOBIOME IN IBS

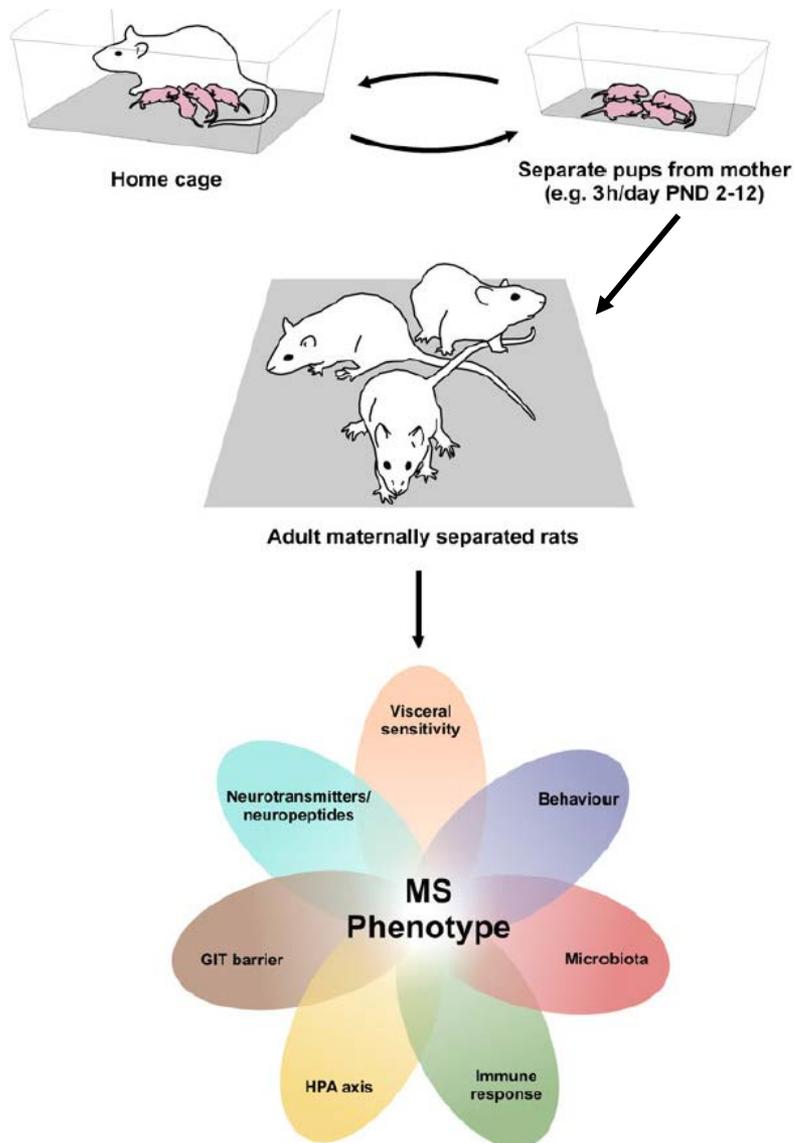
The pathophysiology of IBS



Although the etiology of IBS is not completely understood, several factors are likely to be involved, including:

- 1) Changes in the composition of intestinal microbiota
- 2) Alterations of intestinal epithelial permeability

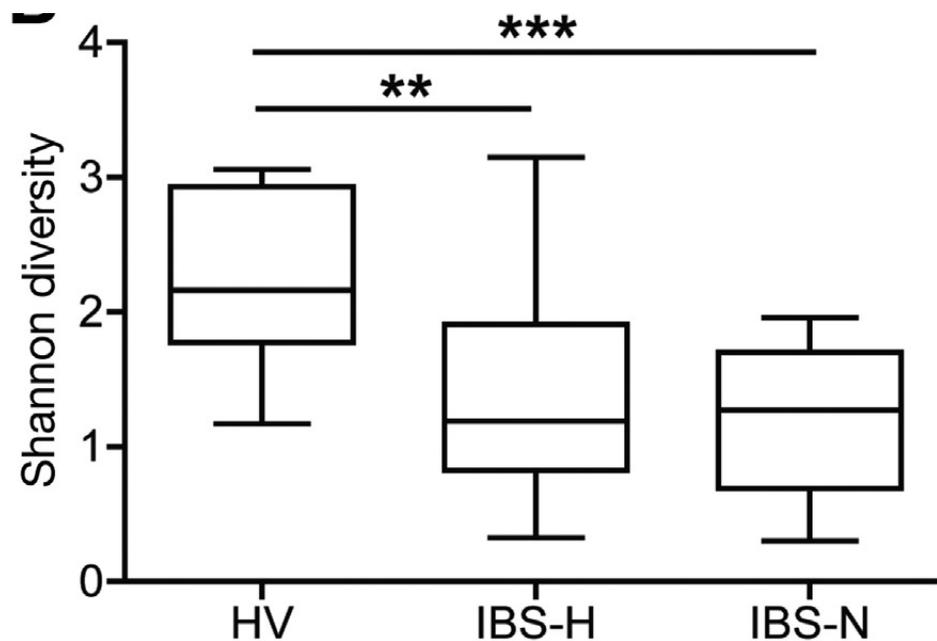
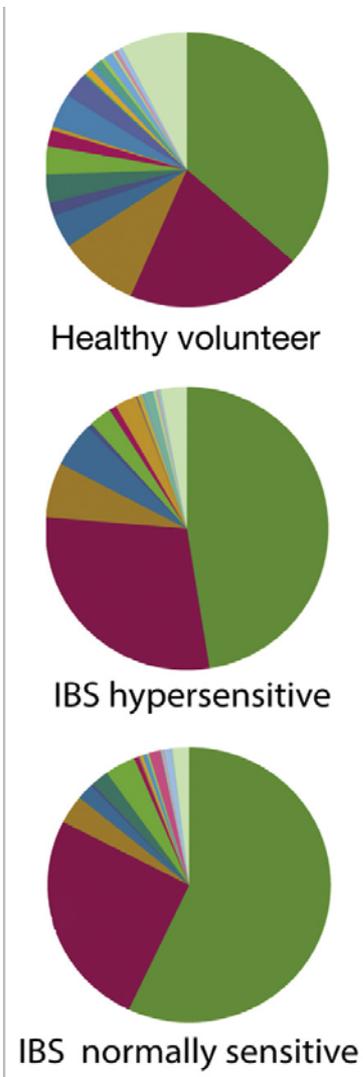
IBS and visceral pain: the model of visceral hypersensitivity in maternal separated rats



- IBS is characterized by a strong stress-related component, which is likely to account for the development of visceral hypersensitivity
- Rats subjected to post natal maternal separation develop visceral hypersensitivity similar to that observed in IBS patients, which becomes evident when subjected to water avoidance (WA) stress
- In addition, these animals display changes in the gut microbiota composition and enhanced permeability of intestinal epithelium

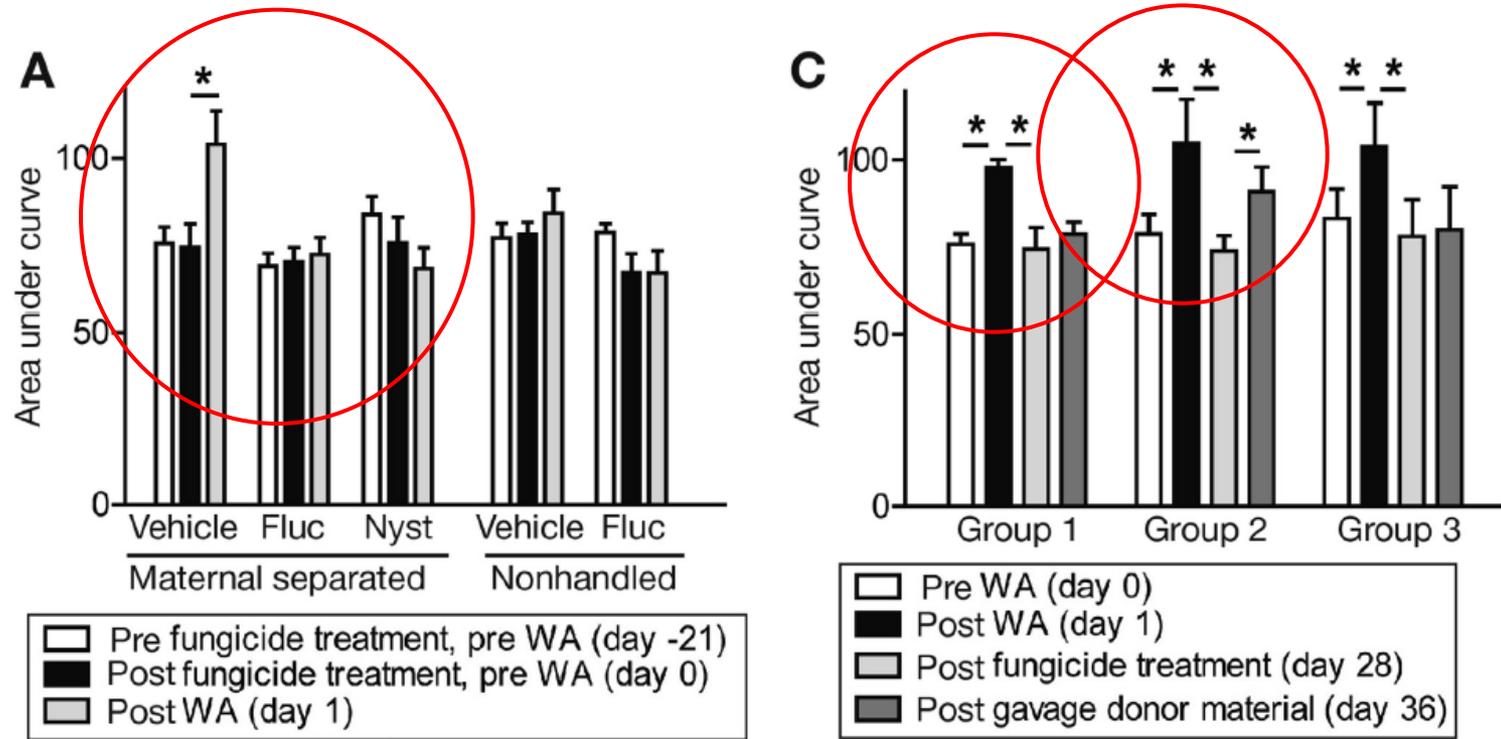
IBS patients display alterations of the intestinal mycobiome composition, as compared with healthy subjects

- Saccharomyces cerevisiae
- Candida albicans
- Aspergillus section Nidulantes
- Debaryomyces prosopidis
- Wallemia muriae
- Torulaspora delbrueckii
- Penicillium section Chrysogena
- Rhodotorula mucilaginosa
- Candida parapsilosis
- Suillus luteus
- Phoma spp.
- Rhodosporidiobolus colostri
- Alternaria alternata
- Alternaria metachromatica
- Verticillium leptobactrum
- Candida humilis
- Hyphodontia pallidula
- Sporobolomyces roseus
- Aspergillus section Aspergillus
- Candida dubliniensis
- unclassified
- Acremonium spp.
- Davidiella tassiana
- Meyerozyma guilliermondii
- Aspergillus section Nidulantes
- Cladosporium cladosporioides compl
- unclassified
- Cyberlindnera c.f. jadinii
- Monographella nivalis
- Wickerhamomyces onychis
- other



Shannon index: combines richness (number) and evenness (relative abundance) of species.

Visceral hypersensitivity is counteracted by antifungal treatment and can be transferred through fecal transplantation



WA: Water Avoidance test (induces visceral hypersensitivity in maternal separated rats)

- **Group 1:** animals receiving fecal material from antifungal-treated maternal separated rats
- **Group 2:** animals receiving fecal material from non-treated maternal separated rats
- **Group 3:** control

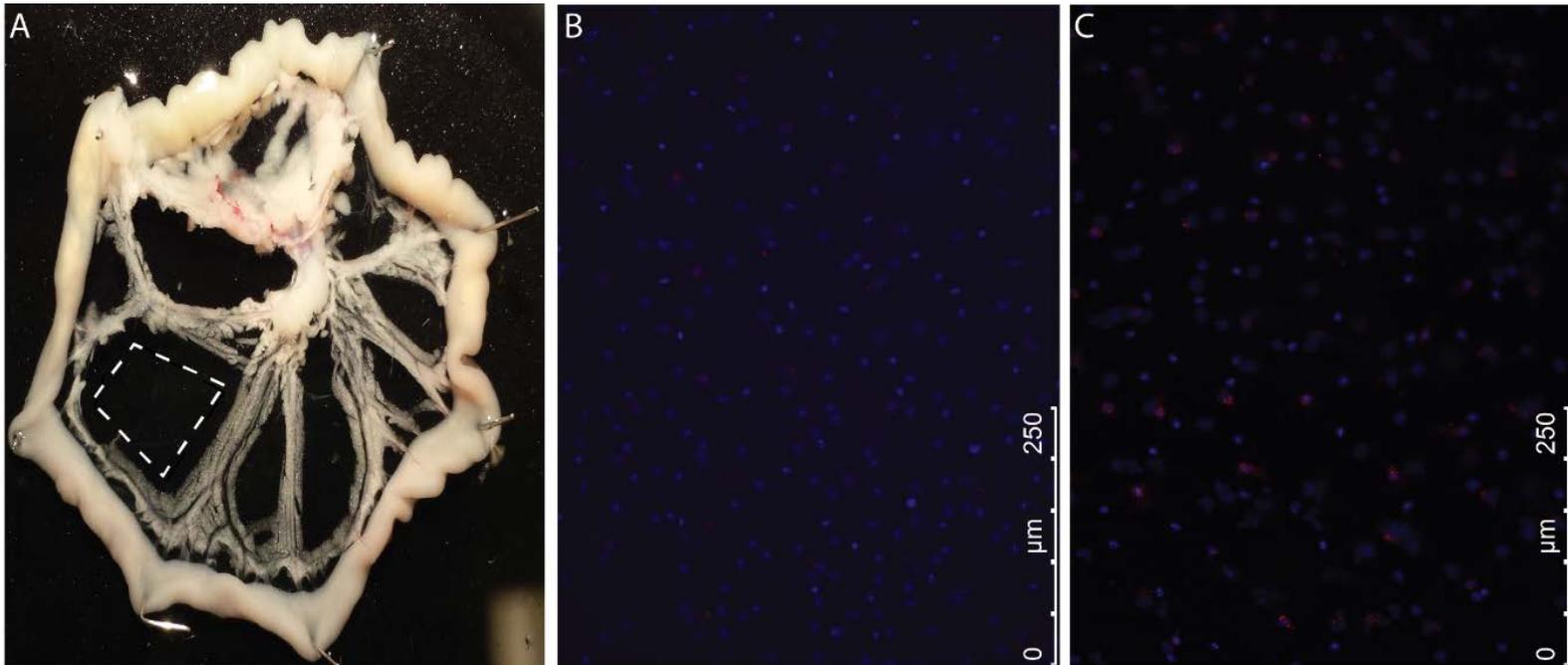
Fungal antigens trigger the release of histamine from mesenteric mast cells in *ex vivo* experiments

Specific staining for degranulating mast cells (texas red)

Rat mesenteric windows

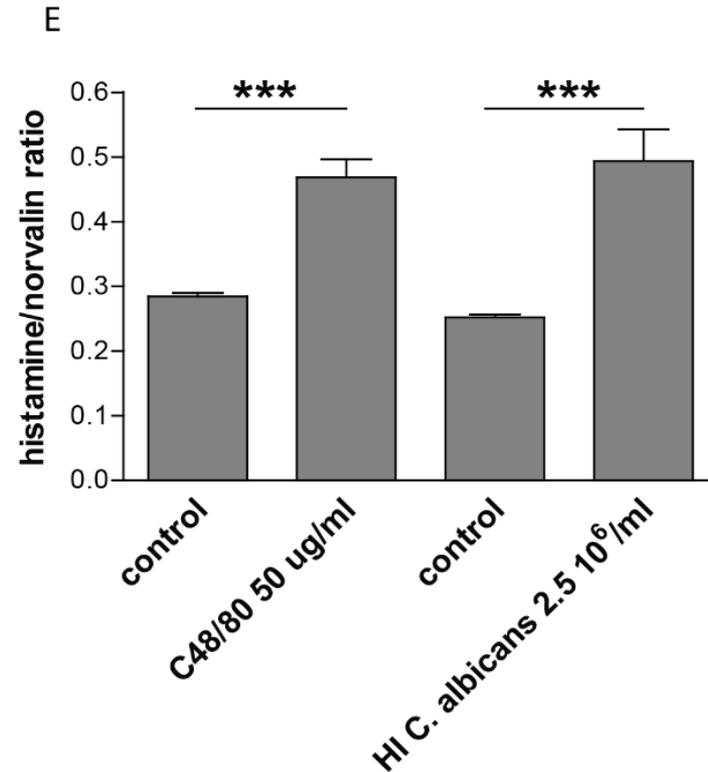
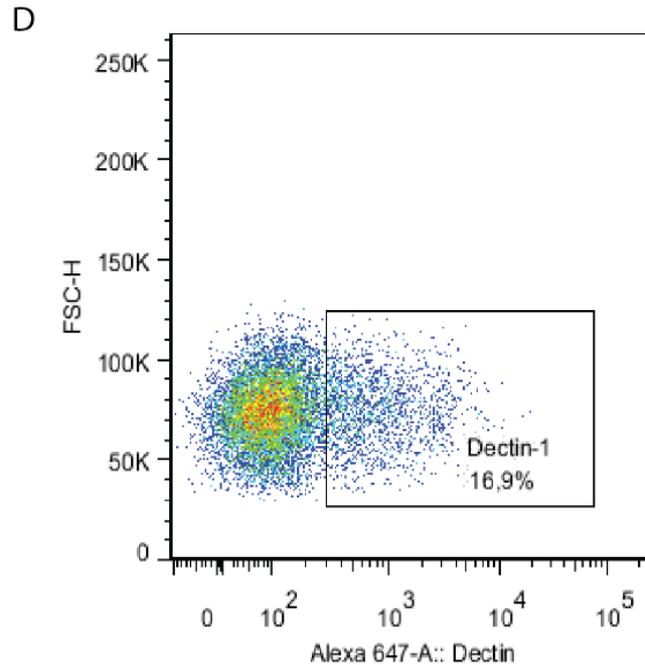
Vehicle

Beta-glucan



The fungal antigen beta-glucan stimulates the degranulation of peritoneal mast cells in rat

Fungal antigens trigger the release of histamine from HMC-1 cultured human mast cell line

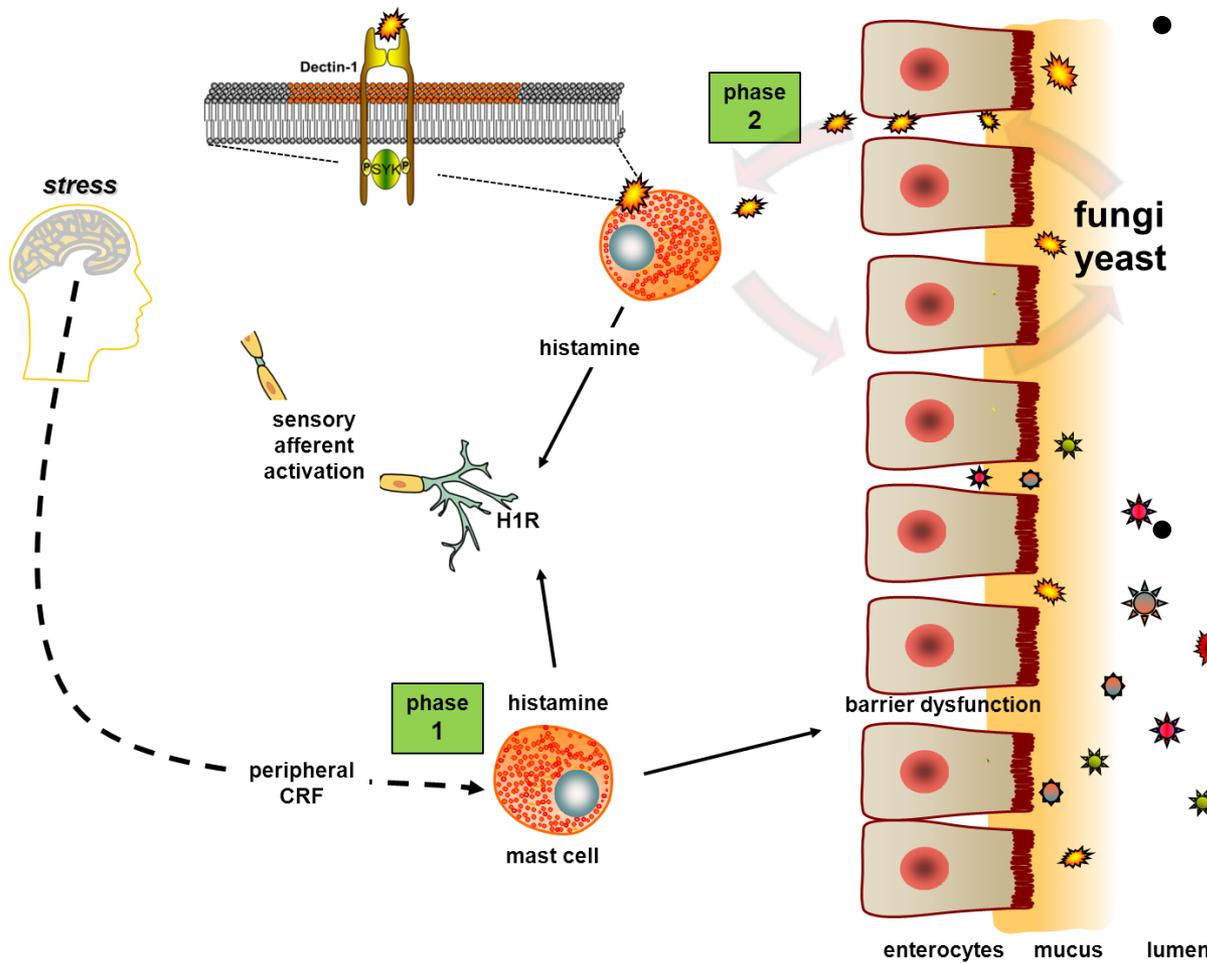


D: a subpopulation of HMC-1 cells express the beta-glucan fungal receptor dectin-1

E: the incubation with *C. albicans* stimulates the histamine release from HMC-1 cells

(C48/80: positive control)

Role of microbiome in visceral hypersensitivity associated with IBS



- Phase 1: the corticotrophin releasing factor (CRF), released in response to stress, activates mast cells and triggers an increase in mucosal permeability
- Phase 2: fungi penetrate through the epithelium and activate mast cells through the dectin-1/Syk pathway to release histamine, which in turn stimulates afferent sensory fibers

CONCLUSIONS

- The research on the role of fungal microbiota in the pathophysiology of digestive diseases is still at the beginning
- However, pre-clinical and clinical evidence suggest an involvement of gut mycobiome in the pathogenesis of IBDs, as well as in visceral pain associated with IBS
- Further research could allow to establish putative therapeutic strategies targeting gut mycobiome for the prevention and treatment of such diseases (i.e. fungal probiotics, such as *S. boulardii*)



“That’s all Folks!”

Isberg[©]

THANK YOU!!