

## Diversity of *Saccharomyces boulardii* CNCM I-745 mechanisms of action against intestinal infections

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### Abstract

The yeast *Saccharomyces boulardii* CNCM I-745 is one of the probiotics recommended for the prevention of antibiotic-associated diarrhea. Studies conducted *in vivo* and *in vitro* demonstrated that in the case of infectious diseases there are two potential sites of action of *Saccharomyces boulardii* CNCM I-745: (1) An action on enteropathogenic microorganisms (adhesion of bacteria and their elimination or an effect on their virulence factors: Toxins, lipopolysaccharide, etc.); and (2) a direct action on the intestinal mucosa (trophic effects, effects on epithelial reconstitution, anti-secretory effects, anti-inflammatory, immunomodulators). Oral administration of *Saccharomyces boulardii* CNCM I-745 to healthy subjects does not alter their microbiota. However, in the case of diseases associated with the use of antibiotics or chronic diarrhea, *Saccharomyces boulardii* CNCM I-745 can restore the intestinal microbiota faster. The interaction of *Saccharomyces boulardii* CNCM I-745 with the innate immune system have been recently demonstrated thus opening up a new therapeutic potential of this yeast in the case of diseases associated with intestinal infections but also other pathologies associated with dysbiosis such as inflammatory diseases.

**Key words:** *Saccharomyces boulardii* CNCM I-745; Probiotics; Yeast; Intestinal infection; Mechanism

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**Core tip:** The efficacy of lyophilized probiotic yeast *Saccharomyces boulardii* CNCM I-745 was clinically demonstrated with controlled studies of intestinal infections associated with antibiotics and acute diarrhea in children. This review summarizes scientific data describing the mechanism of *Saccharomyces boulardii* protection against infection and emphasizes the diversity of potential mechanism of action that this

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probiotic yeast can have against pathogenic microorganisms. More recently, effects on the recovery of the intestinal microbiota as well as on the immune system have been demonstrated, thus opening up a new therapeutic potential of this yeast.

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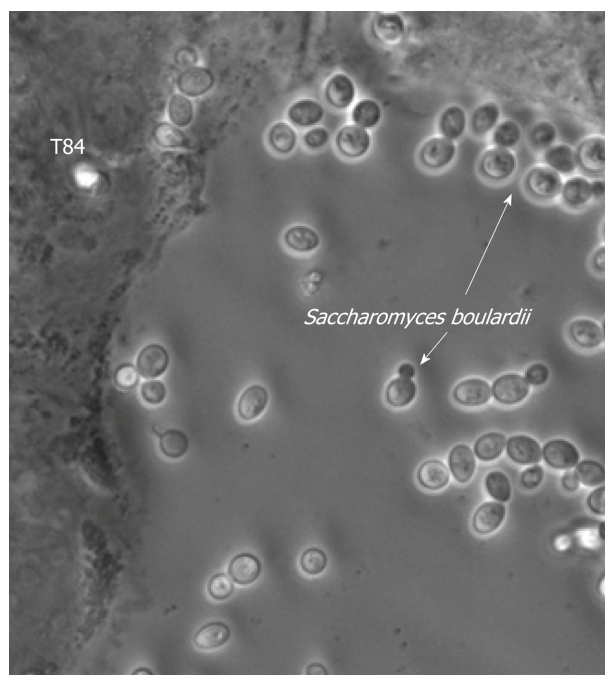
## INTRODUCTION

Probiotics are living microorganisms that when administered in adequate amounts have a beneficial effect on the host. Most are bacteria, the best known of which are strains of *Lactobacillus* spp., and *Bifidobacterium* spp. However, there is a non-bacterial microorganism classified as a probiotic agent: this is the yeast *Saccharomyces boulardii* (*S. boulardii*) CNCM I-745 (Figure 1). *S. boulardii* was discovered by the French microbiologist Henri Boulard in 1920 during a visit to Indochina. The microbiologist noted that people who drank a decoction prepared from the outer skin of the lychee and mangosteen fruits did not develop diarrhea. He isolated the causative agent and named it *S. boulardii*. The initial strain was deposited at the National Collection of Microorganism Culture (CNCM) at the Institut Pasteur under the reference CNCM I-745. As a yeast, *S. boulardii* CNCM I-745 differs from bacterial probiotics in size, cell wall composition, antibiotic resistance and metabolic properties<sup>[1,2]</sup>. *S. boulardii* CNCM I-745 is the first identified yeast that has been studied for use as a probiotic in human medicine. This strain responds to a manufacturing process and a mode of conditioning that preserves the characteristics of the initial strain and its viability. The probiotic actions demonstrated by this strain of yeast are not extrapolatable to other strains. The aim of this review is to synthesize the experimental studies that have been carried out with the yeast *S. boulardii* strain CNCM I-745 in order to understand its mechanism of action against pathogenic microorganisms.

## CLINICAL DATA IN THE CASE OF INFECTIOUS DIARRHEA

*S. boulardii* strain CNCM I-745 is prescribed in adults and children for the prevention and treatment of diarrhea, including antibiotic and post-antibiotic diarrhea associated with *Clostridium difficile* (*C. difficile*). Three prospective, randomized, double-blind, placebo-controlled clinical trials demonstrated the efficacy of *S. boulardii* CNCM I-745 in preventing diarrhea associated with antibiotic therapy in adults<sup>[3-5]</sup>. In children, two studies showed that *S. boulardii* CNCM I-745 has a preventive effect in diarrhea associated with antibiotics<sup>[6,7]</sup>; the second study also demonstrated a curative effect. A recently published meta-analysis<sup>[8]</sup> analyzed data from 21 randomized studies comprising a total of 4780 adult or child patients that received antibiotics. The results of this study support those of the first meta-analysis conducted in 2005<sup>[9]</sup> and show an efficacy of *S. boulardii* CNCM I-745 in the pediatric and adult population regardless of the type of antibiotic prescribed. When considering studies that reveal a significant benefit of the administration of *S. boulardii* strain CNCM I-745, an early treatment with the yeast during antibiotic therapy appears to be an essential factor with the administration of *S. boulardii* strain CNCM I-745 for the entire duration of antibiotic treatment. Several clinical studies show the effectiveness of *S. boulardii* CNCM I-745 in relapsing colitis and *C. difficile* diarrhea<sup>[10-12]</sup>. There are several studies evaluating *S. boulardii* CNCM I-745 in patients with gastroenteritis that may be due to a viral, bacterial, or parasitic infection. A 2012 meta-analysis of 11 randomized controlled trials found that *S. boulardii* decreased the duration of diarrhea and hospitalization due to gastroenteritis in all countries examined<sup>[13-18]</sup>.

Tourists traveling to countries with warm climates, particularly in tropical or subtropical regions, are at high risk of diarrhea. In 80% to 85% of cases, diarrhea is due to pathogenic bacteria [*Escherichia coli* (*E. coli*), enteropathogenic, *Campylobacter jejuni*, *Shigella*, *Salmonella*, *Yersinia enterocolitica*]. Viruses [Norwalk or Rotavirus (RV)] and parasites [*Entamoeba histolytica* (*E. histolytica*), *Giardia lamblia*, *Cyclospora*, *Cryptosporidium*] are less frequently the causative pathogen. In many cases, the cause



**Figure 1** Transmission microscopy image showing *Saccharomyces boulardii* CNCM I-745 on a culture of human epithelial cells (T84 lineages). (Source: Pontier-Bres R and Czerucka D). The arrows indicate budding yeast located either in the spaces between the cells or near the cell walls and the formation of a protective barrier.

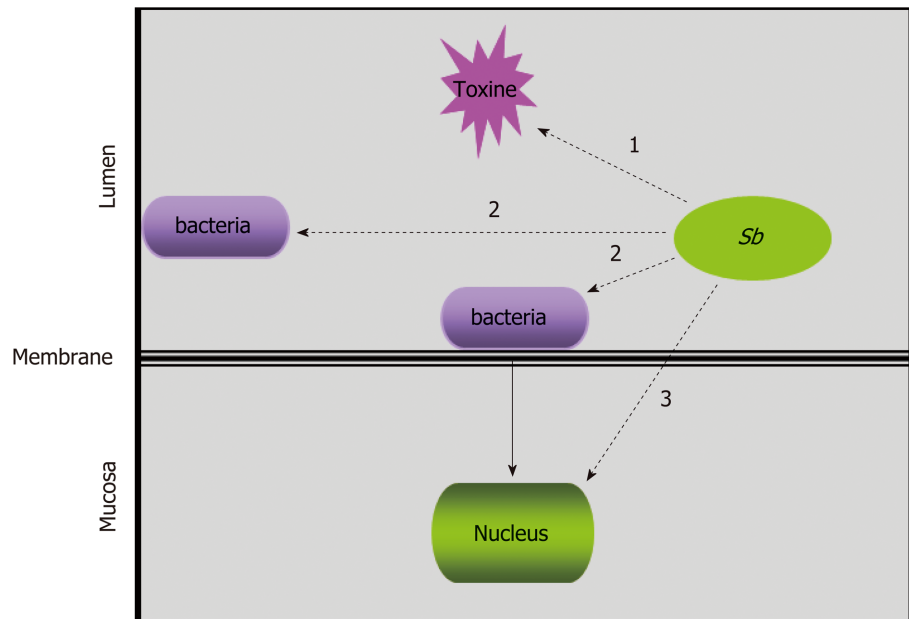
can not be determined. Two randomized controlled studies were conducted with *S. boulardii* CNCM I-745 with a total of four treatment arms with different doses. Kollaritsch *et al*<sup>[19]</sup> analyzed the results from 1231 Austrian travelers that were randomized into 2 arms, receiving *S. boulardii* CNCM I-745 at two different doses (250 and 500 mg daily) or a placebo for 3 wk. This treatment was started 5 d prior to the trip and continued throughout the trip. In the placebo group, the rate of diarrhea was 43% while it was 34% for the traveler receiving 250 mg of *S. boulardii* CNCM I-745 and 32% for those receiving the highest dose. No side effects have been reported<sup>[19]</sup>. In a second study by Kollaritsch *et al*<sup>[20]</sup> conducted with 3000 Austrian tourists, travelers received either a dose of *S. boulardii* CNCM I-745 (250 mg or 1 g per day) or a placebo. The treatment was initiated 5 days prior to departure and continued throughout the trip (for a mean duration of 3 wk). Patients that received a placebo had a higher frequency of diarrhea (39% *vs* 34% for the low dose and 29% for the high dose,  $P < 0.05$ ).

## PRECLINICAL-STUDIES: EFFECTS ON ENTEROPATHOGENIC MICROORGANISMS

Several studies using animal or cellular models have shown that *S. boulardii* CNCM I-745 has a beneficial effect against infections by various pathogenic bacteria such as *C. difficile*, *Vibrio cholerae*, *Salmonella*, *Shigella*, *E. coli*, viruses (RV) and finally, pathogenic yeasts, for example *C. albicans*. *S. boulardii* CNCM I-745 acts either directly on bacterial toxins or on the pathogen, and can also act directly on the intestinal mucosa of the host and modulate the response to infection (Figure 2). The protective action of *S. boulardii* CNCM I-745 with respect to an infection often results from the complementary effect of several mechanisms.

### Anti-toxin activity

**Vibrio cholerae:** The first studies on the mechanism of action of *S. boulardii* CNCM I-745 with respect to pathogenic bacteria focused on the *Vibrio cholerae*. In 1986, Vidon *et al*<sup>[21]</sup> demonstrated, *in vivo*, that the administration of *S. boulardii* CNCM I-745 to ligated jejunal loop in rats that had been inoculated with cholera toxin (CT) significantly reduced the fluid and sodium secretion induced by CT. This effect has been confirmed in models of intestinal epithelial cells<sup>[22,23]</sup>. The action of *S. boulardii* CNCM I-745 (Figure 3A) is associated with a decrease in CT-induced cAMP. It requires live yeasts and it is associated to a protein factor present in the culture

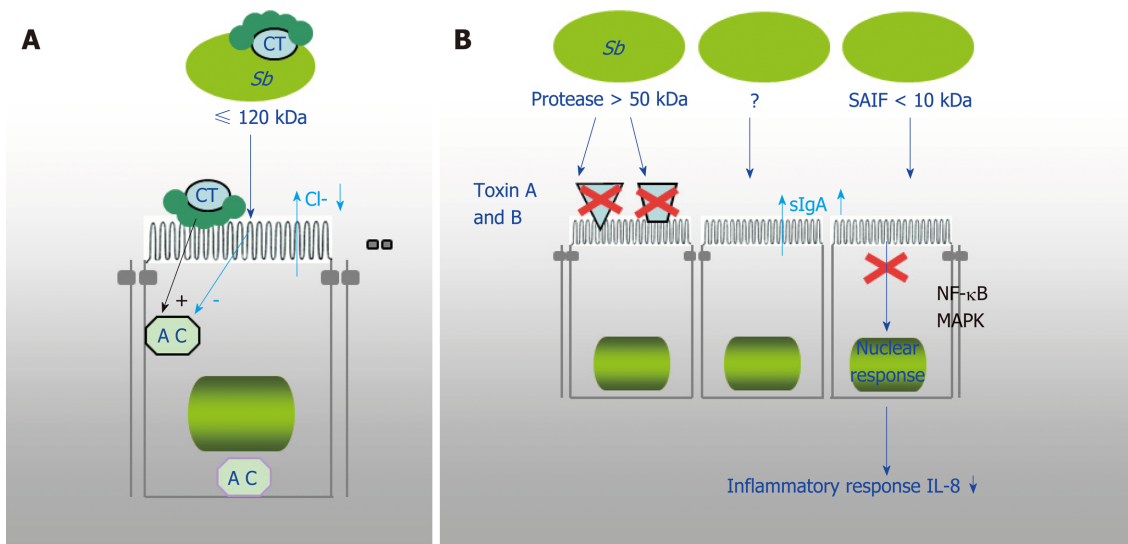


**Figure 2** The hypothesized targets of *Saccharomyces boulardii* CNCM I-745 during bacterial infections: *Saccharomyces boulardii* CNCM I-745 may act directly on toxins “1”, on pathogenic bacteria “2” or on host cells “3”. Sb: *Saccharomyces boulardii* CNCM I-745.

supernatant of *S. boulardii* CNCM I-745. This protein factor, at 120 kDa, acts directly on enterocytes by inhibiting the cAMP-induced secretion of chloride (Cl<sup>-</sup>) triggered by CT, and also by other cAMP-agonists like Vaso-intestinal peptide (VIP) or the Labile toxin (LT) of *E. coli*<sup>[22,23]</sup>. Another study shows that *S. boulardii* CNCM I-745 can attach CT to its cell wall, which is another mechanism of action against this toxin<sup>[24]</sup>.

***Clostridium difficile*:** The mechanism of action of *S. boulardii* CNCM I-745 with respect to *C. difficile* infections has been the most studied. The administration of *S. boulardii* CNCM I-745 significantly reduces the mortality induced by *C. difficile* colitis in clindamycin-treated hamsters<sup>[25]</sup> and mice inoculated either by *C. difficile*<sup>[26]</sup> or by toxins A and B produced by the bacteria<sup>[27]</sup>. A recent study demonstrated the protective effect of *S. boulardii* CNCM I-745 against different ribotypes of *C. difficile* that are associated with outbreaks<sup>[28]</sup>. Among the various mechanisms of action proposed (action on the bacterium or its toxins see **Figure 3B**), the direct action of *S. boulardii* CNCM I-745 on toxins A and B of *C. difficile* and their receptors is the most supported. In fact, the injection of toxin A into the ileal loop does not induce inflammatory diarrhea if the animal has been previously treated with *S. boulardii* CNCM I-745 or its supernatant<sup>[29]</sup>. *In vitro* studies have shown that the culture supernatant of *S. boulardii* CNCM I-745 inhibits the adhesion of toxin A to its receptor<sup>[30]</sup>. A 54kDa protease identified in this supernatant can degrade *C. difficile* toxins A and B and their receptors<sup>[29,30]</sup>. The inflammation associated with *C. difficile* colitis is due to the activation of pro-inflammatory pathways by toxins A and B: nuclear translocation of NF- $\kappa$ B factor and activation by phosphorylation of MAP kinases that induce cytokine synthesis. The culture supernatant of *S. boulardii* CNCM I-745 inhibits interleukin 8 (IL-8) synthesis as well as nuclear translocation of NF- $\kappa$ B and inhibits toxin A-induced phosphorylation of ERK1/ 2 and JNK in epithelial cells<sup>[31]</sup>. In addition to acting on toxins and their receptors, the mechanism of action of *S. boulardii* CNCM I-745 with respect to *C. difficile* infections appears to involve modulation of the immune system. In fact, *S. boulardii* CNCM I-745 increases the level of circulating anti-toxin A IgA in mice that have been stimulated with inactivated toxin A<sup>[32]</sup>.

***Bacillus anthracis*:** *Bacillus anthracis*, the etiological agent of anthrax, infects the host by three routes of entry: cutaneous (most common), digestive and inhalation. The virulence factors are the capsule responsible for sepsis and two toxins responsible for toxemia. The toxins are composed of three peptides: The protective antigen (PA) and two enzymatic factors. The PA binds to cell-surface receptors and, after endocytosis, injects into the cytosol the two enzymatic factors: The lethal factor (LF) and the edematogenic factor (EF). The lethal toxin (LT) formed by the combination of PA with LF is a 90 kDa protein with metalloprotease activity that specifically cleaves MEK-2



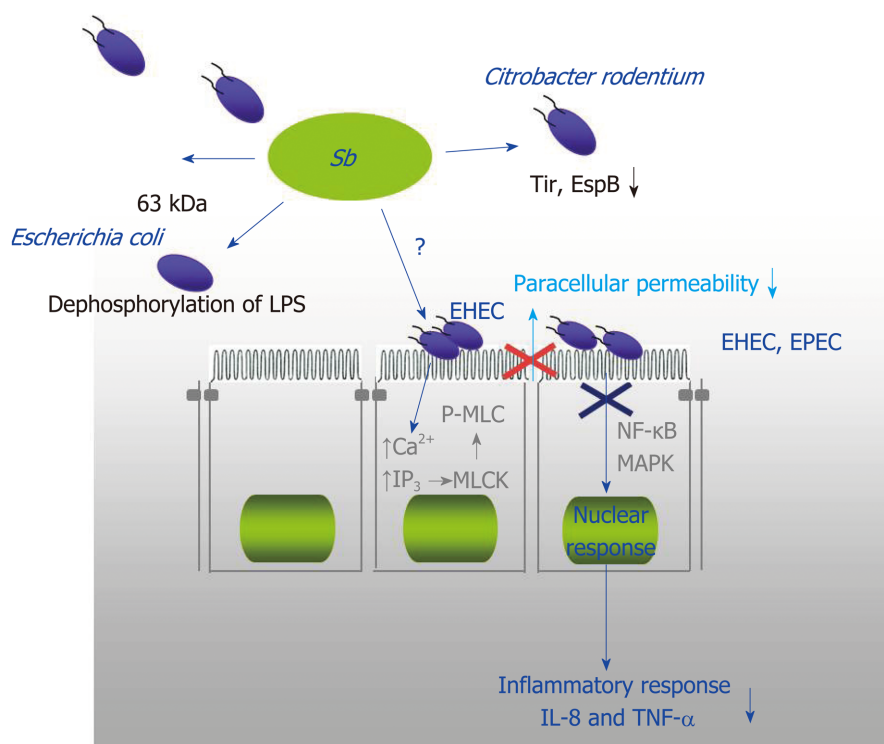
**Figure 3 Demonstrated mechanism of *Saccharomyces boulardii* CNCM I-745 action against bacterial toxins.** A: *Saccharomyces boulardii* CNCM I-745 (*S. b*) produces a 120 kDa protein that inhibits adenylate cyclase and cholera toxin (CT)-induced chloride secretion. *S. boulardii* CNCM I-745 can also bind to CT; B: *S. boulardii* CNCM I-745 secretes a protease (> 54kDa) that lyses *C. difficile* toxins A and B and their receptors and a protein (< 10 kDa) that inhibits the signaling pathways involved in interleukin 8 synthesis. AC: Adenylate cyclase; CT: Cholera toxin; Sb: *Saccharomyces boulardii* CNCM I-745; IL-8: Interleukin 8.

protein kinase. This toxin affects actin filaments in endothelial and epithelial cells and triggers morphological changes that result in the opening of tight junctions. Incubating cells with *S. boulardii* CNCM I-745 prior to exposure to LT toxin maintains the structure of the actin fibers and junctions<sup>[33]</sup>. Furthermore, the cleavage of MEK-2 is delayed in the presence of *S. boulardii* CNCM I-745. The yeast acts directly on the LT subunits by cleaving the PA antigen and attaching the antigen and LF to its surface. These results suggest the use of *S. boulardii* CNCM I-745 as a preventive agent for *B. anthracis* infection.

### Action on pathogenic bacteria

**Enteropathogenic *E. coli* and enterohaemorrhagic *E. coli*:** Among pathogenic *E. coli*, enteropathogenic *coli* (EPEC) cause infectious diarrhea in developing countries, while enterohaemorrhagic *coli* (EHEC), that produce the shiga-like toxin, are involved in foodborne infections in industrialized countries. The adhesion of these bacteria to the intestinal mucosa is a crucial step in their pathogenicity. After contact with the mucosa, these bacteria inject effector proteins into the host through the type III secretion system. These effector proteins induce changes in the structure of tight junctions, stimulate the activation of MAP kinases and the factor NF-κB and, consequently, activate the synthesis of IL-8. Studies on monolayers of polarized human epithelial cells (Figure 4) showed that incubation with *S. boulardii* CNCM I-745 prevents the increase in intestinal permeability induced by EPEC and EHEC infection<sup>[34,35]</sup>. In addition, the structure of the tight junctions is maintained in these infected cells after exposure to the yeast. In EHEC-infected cells, *S. boulardii* CNCM I-745 inhibits phosphorylation of the myosin light chain that is directly involved in maintaining the integrity of tight junctions. *S. boulardii* CNCM I-745 also has an anti-inflammatory effect that inhibits the activation of mitogen-activated protein kinases, the nuclear translocation of NF-κB, and, consequently, the synthesis of IL-8<sup>[34,35]</sup>. In a mouse model infected with *Citrobacter rodentium* (the equivalent of EPEC in rodents) *S. boulardii* CNCM I-745 decreases the flux of mannitol and improves the histological score of infected animals<sup>[36]</sup>. *In vivo* the yeast acts directly on the expression of the virulence factors of the bacterium: Tir (Translocated receptor intimin), a factor directly involved in the adhesion of bacteria to the surface of enterocytes, and EspB, an effector protein injected into the host cell by the type III secretion system. Another study shows that *S. boulardii* CNCM I-745 can act on bacterial factors, in this case lipopolysaccharide (LPS) of *E. coli*. Buts et al<sup>[37]</sup> reported that *S. boulardii* CNCM I-745-synthesized phosphatase could de-phosphorylate *E. coli* O55B5 LPS. Injection to rats of LPS exposed to phosphatase purified from *S. boulardii* CNCM I-745 resulted in a reduction in circulating TNF-compared to the level induced by untreated LPS.

***Salmonella enterica* Typhimurium and *Shigella flexneri*:** Ingestion of food contaminated with *Salmonella enterica* Serovar Typhimurium (hereafter referred to as *Salmonella typhimurium*) results in diarrhea. *Salmonella typhimurium* are invasive



**Figure 4** The protective mechanisms against enteropathogenic *Escherichia coli* (enteropathogenic coli, enterohaemorrhagic coli and *Citrobacter rodentium*). They include an effect on the mucosa with *Saccharomyces boulardii* CNCM I-745 inhibiting the pathways involved in opening tight junctions (phosphorylation of myosin light chain kinase), inhibition of activation pathways of mitogen-activated protein kinases and NF-κB that are involved in the synthesis of Interleukin 8, and finally a direct effect of *S. boulardii* CNCM I-745 on bacteria (dephosphorylation of lipopolysaccharide of *Escherichia coli* and modification of the expression of pathogenicity factors of *Citrobacter rodentium*). EHEC: Enterohaemorrhagic coli; EPEC: Enteropathogenic coli; LPS: Lipopolysaccharide; MAPK: Mitogen-activated protein kinase; MLCK: Myosin light chain kinase; P-MLC: Phosphorylation of myosin light chain; IL-8: Interleukin 8; TNF-α: Tumor necrosis factor α Sb: *Saccharomyces boulardii* CNCM I-745.

bacteria that use several entry routes into the mucosa: microfold cells, enterocytes and a specific population of dendritic cells (DC). These bacteria are also able to induce a pro-inflammatory response by activating the MAP kinase and NF-κB pathways. Inoculation of *S. boulardii* CNCM I-745 to gnotoxenic or conventional mice infected with *Salmonella typhimurium* or *Shigella flexneri* protects against mortality (*Shigella flexneri*) or reduces the severity of intestinal lesions (*Salmonella typhimurium*)<sup>[38]</sup>. This protective effect is not related to a reduction in the level of intestinal population of these bacteria. In the case of *Salmonella* infection, the protective effect of *S. boulardii* CNCM I-745 has been confirmed in a conventional mouse model and a mouse model with intestinal flora impaired by antibiotic treatment<sup>[39,40]</sup>. In treated animals, mortality and translocation of *S. typhimurium* to the liver and spleen were reduced. *In vitro*, *S. boulardii* CNCM I-745 decreases enterocyte invasion by *S. typhimurium*, which is correlated with decreased activation of the Rac pathway, a pathway directly used during invasion by these bacteria (Figure 5)<sup>[39]</sup>. *S. typhimurium*, like *E. coli*, are peritrichous bacteria with flagella that give them the ability to swim. Mutants devoid of flagellum are immobile and not invasive. A recent study showed that *S. boulardii* CNCM I-745 modifies the motility of bacteria by a steric effect and also by chemotaxis, decreasing the invasiveness of *S. typhimurium*<sup>[41]</sup>. In polarized T84 cells, *S. boulardii* CNCM I-745 maintains the structure of tight junctions in infected monolayers. In addition, in this model, the yeast prevents the activation of NF-κB and MAP kinase pathways and the synthesis of IL-8, which are associated with cell infection. The maintenance of tight junctions and the anti-inflammatory effect of *S. boulardii* CNCM I-745 were also confirmed in the case of *Shigella* infection<sup>[42]</sup>. The adhesion of *E. coli* and *Salmonella* to *S. boulardii* CNCM I-745 cell walls was reported in an earlier study<sup>[43]</sup> and has recently been confirmed *in vitro* and *in vivo* for *S. typhimurium* by scanning and confocal microscopy<sup>[39,40]</sup>. *Salmonella* adherent to the yeast wall was visualized by confocal microscopy on sections of caecum (Figure 6). The adhesion constitutes one of the mechanisms of action of *S. boulardii* CNCM I-745. By imaging

bioluminescent *S. typhimurium*, it was shown that *in vivo* *S. boulardii* CNCM I-745 modifies bacterial propagation in the gut of living mice during the first hours of infection. The yeast accelerates the spread of Salmonella along the digestive tract with the bacteria being detected in the feces as early as 6 h after the onset of infection. In addition, the administration of *S. boulardii* CNCM I-745 modifies the site-dependent (ileum vs caecum) pro and anti-inflammatory responses at the early stages of infection<sup>[40]</sup>.

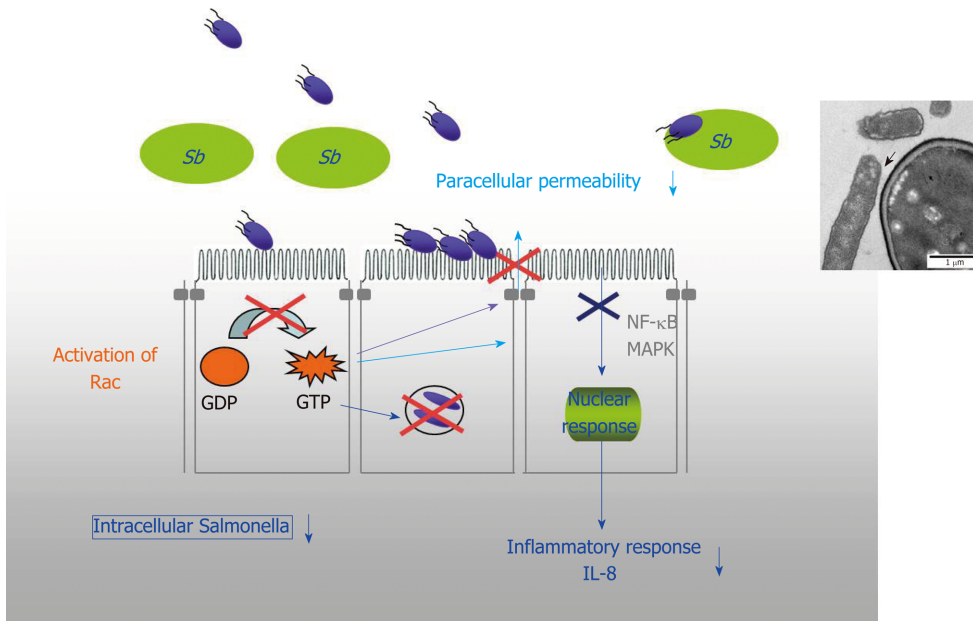
**Helicobacter pylori:** *Helicobacter pylori* (*H. pylori*) is major causative agent of gastritis, peptic ulcer disease and is strongly associated with gastric cancer and lymphoma of the gastric mucosa-associated lymphoid tissue. Currently recommended treatments for the eradication of *H. pylori* is standard triple therapy combining two antibiotics with a proton pump inhibitor. This therapy produces excellent cure rates but present side effects such as (diarrhoe, nausea/vomiting and even *C. difficile* infection) and emergence of antibiotic-resistant strains. Introduction of probiotics, especially *S. boulardii* as adjuvant treatment show promising results in reducing side effect<sup>[44,45]</sup>. Investigation on *S. boulardii*'s mechanism of action demonstrated that this yeast prevents binding of *H. pylori* on duodenal cells, whereas bacterial probiotic strains do not. It may be linked with *S. boulardii* neuramidase activity that modifies *H. pylori* binding site on the duodenal cells<sup>[46]</sup>. In a murine model of Helicobacter infection using a close species of *H. pylori* (*H. suis*), *S. boulardii* decreased the Helicobacter bacterial load, inhibited the formation of lymphoid follicles and reduced expression levels of inflammatory cytokines and chemokines in the stomach. It also increased the production of anti-helicobacter specific IgA and sIgA and beta-defensin in the small intestine after the infection<sup>[47]</sup>.

#### Action on other pathogenic microorganisms

**Candida albicans:** *Candida albicans* (*C. albicans*) is the most commonly isolated opportunistic pathogenic fungus in humans, responsible for localized and systemic infections. The prevention of *C. albicans* infections is one of the first effects attributed to *S. boulardii* CNCM I-745<sup>[48]</sup>. In the gnotoxenic mouse, continued administration of *S. boulardii* CNCM I-745 precludes the implantation of a strain of *C. albicans* in the gastrointestinal tract<sup>[49]</sup>. Two studies in immunocompromised mice and rats indicate that *S. boulardii* CNCM I-745 also reduces the translocation of *C. albicans* to mesenteric lymph nodes (MLN)<sup>[50,51]</sup>. In a mouse model of dextran sulfate sodium- induced colitis, *S. boulardii* CNCM I-745 reduced both inflammation and intestinal colonization by *C. albicans*<sup>[52]</sup>. The antagonistic effects of *S. boulardii* CNCM I-745 on *C. albicans* have recently been demonstrated *in vitro*<sup>[53]</sup>. *S. boulardii* CNCM I-745 has an inhibitory effect on the filamentous growth of *C. albicans*, as well as its adhesion and the formation of biofilm on different surfaces. The same authors identified the active compound as capric acid, an AGCC synthesized by *S. boulardii* CNCM I-745, which reduces the virulence of *C. albicans*<sup>[54]</sup>. *In vitro*, *S. boulardii* CNCM I-745 decreases the adhesion of *C. albicans* to Caco-2 and Intestin 407 cells, and inhibits IL-8 expression<sup>[55]</sup>. *S. boulardii* CNCM I-745 also shows an anti-inflammatory effect in intraepithelial lymphocytes, of a mouse model, that were exposed to *C. albicans*<sup>[56]</sup>. In the presence of the yeast, the authors observed an increase in the anti-inflammatory cytokines IL-4 and IL-10, and a decrease in the pro-inflammatory cytokine IL-1.

**Rotavirus:** Rotavirus (RV) infection is the most frequent and severe form of acute gastroenteritis in infants and children worldwide, and frequently requires hospitalization. RV infects mature enterocytes of the small intestinal villi, inducing broad functional and structural damage. In humans, RV causes watery diarrhea that results from a combination of osmotic and secretory effects. The non-structural protein 4 (NSP4) produced by RV plays a key role in secretory diarrhea by inducing a redox imbalance, resulting in the secretion of chloride by intestinal epithelial cells. In Caco-2 cells infected with the viral strain SA11, the secretion of chloride is induced in association with an increase in reactive oxygen species<sup>[57]</sup>. The supernatant of *S. boulardii* CNCM I-745 reduces oxidative stress in these cells and strongly inhibits RV-induced chloride secretion. These results were confirmed on human intestinal biopsies exposed to NSP4. *S. boulardii* CNCM I-745, via a soluble metabolite, prevents oxidative stress and inhibits NSP4-induced chloride secretion<sup>[57]</sup>.

**Entamoeba histolytica:** Amoebiasis ranks third among the most deadly parasitic diseases in the world. About 10% of the world's population is infected with amoeba parasites of the genus *Entamoeba*, the most pathogenic of which is *E. histolytica*. It is a protozoan that can surround itself with a thin shell to form a cyst a few microns in diameter. When these cysts are ingested, they germinate in the small intestine to give rise to the vegetative form, the trophozoites, which enter the large intestine, proliferate and re-encysted. It is in this form that *E. histolytica* is expelled in feces and is



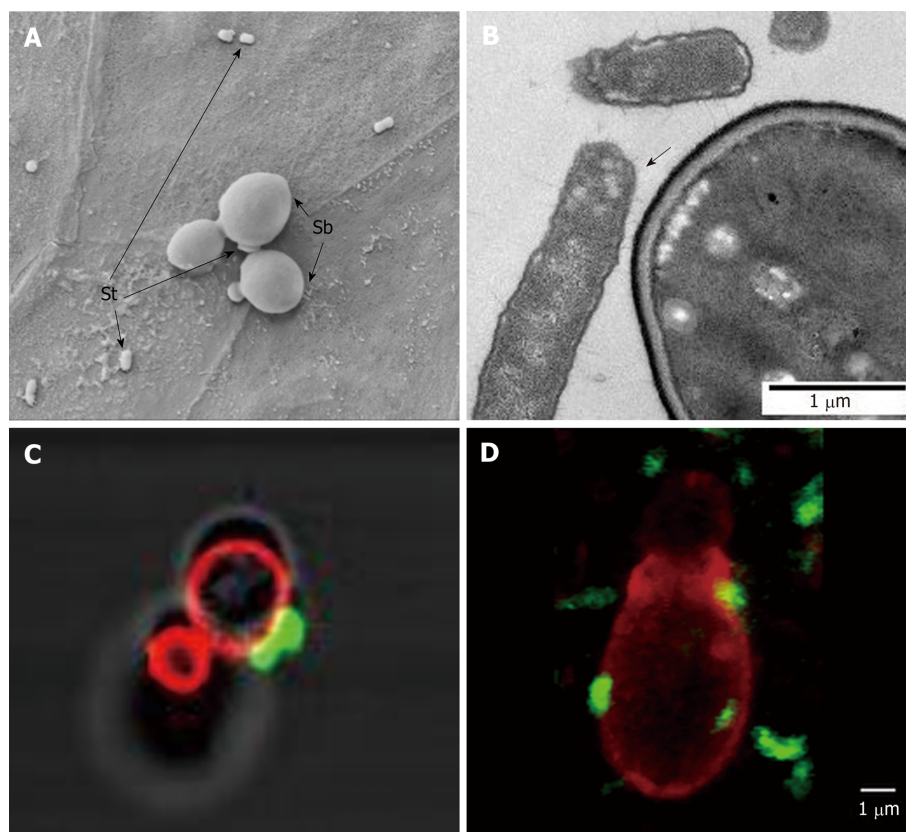
**Figure 5** The mechanisms of protection against enteroinvasive bacteria (*Salmonella* and *Shigella*). In the case of *Salmonella*, there is a decrease in the activation of the small GTPase pathway and consequently a decrease in the number of intracellular bacteria and the maintenance of tight junctions. *Saccharomyces boulardii* CNCM I-745 also induces inhibition of mitogen-activated protein kinases and NF- $\kappa$ B activation pathways that are involved in interleukin 8 synthesis. And finally, a direct effect of *S. boulardii* CNCM I-745 on bacteria with the modification of their motility and the adhesion of *Salmonella* to *S. boulardii* CNCM I-745. IL-8: Interleukin 8; MAPK: Mitogen-activated protein kinase; Sb: *Saccharomyces boulardii* CNCM I-745.

likely to contaminate other people. If the infection remains generally asymptomatic, the parasite can, however, cause painful and bloody diarrhea (amoebic dysentery), ulcers, and, in the more severe forms, lead to abscesses in the liver, lungs and brain. In young rats, infection with this species can produce lesions similar to those observed in humans. A model of caecal amoebiasis in rat was used to study the effect of *S. boulardii* CNCM I-745 on the development of lesions<sup>[58]</sup>. In this model, young rats infected with *E. histolytica* were treated with *S. boulardii* CNCM I-745. In the yeast treated group the number of sick pups was significantly lower and the macroscopic appearance of the lesions on the cecum, as well as the presence of amoebae, was decreased. The lesions were similar to those of the control animals, but their healing process was accelerated. In addition, *S. boulardii* CNCM I-745 showed no amoebicidal activity. The antagonistic effect of the yeast has been explained *in vitro* by competition between the yeast and amoebae at binding sites on erythrocytes<sup>[59]</sup>.

## EFFECT ON MUCOSA THAT CAN BE IMPLICATED IN THE ANTI-PATHOGENIC EFFECT ANTI-SECRETORY EFFECTS

Intestinal fluid secretion is driven by active  $\text{Cl}^-$  secretion creating the electro-chemical gradient for paracellular  $\text{Na}^+$  secretion and the osmotic driving force for transcellular water secretion.  $\text{Cl}^-$  is transported into the cell at the basolateral membrane by a  $\text{Na}^+/\text{K}^+/\text{Cl}^-$  cotransporter which is driven by  $\text{Na}^+$  and  $\text{Cl}^-$  concentration gradients produced by  $\text{Na}^+\text{K}^+$ -ATPase and basolateral  $\text{K}^+$  channels. The electrochemical gradient drives  $\text{Cl}^-$  secretion across the luminal membrane by two  $\text{Cl}^-$  channels: (1) The cAMP-activated channel CFTR; and (2) the  $\text{Ca}^{2+}$ -activated channel. These channels are an attractive target for potentially antidiarrheal therapeutics. The effect of *S. boulardii* CNCM I-745 on these channels has been the subject of several studies using pharmacological agents. The first study conducted in the jejunum of pigs or in tissue from animals treated with *S. boulardii* CNCM I-745, shows a decrease in  $\text{Cl}^-$  secretion induced by a phosphodiesterase inhibitor: Theophylline<sup>[60]</sup>. Another study performed *in vitro* reports that *S. boulardii* CNCM I-745 inhibits the secretion induced by receptor (vasointestinal peptide or prostaglandin E2) or non-receptor (forskolin) c-AMP mediated  $\text{Cl}^-$  secretion, thus demonstrating that *S. boulardii* CNCM I-745 can directly affect adenylate cyclase activity<sup>[22]</sup>. In the same study *S. boulardii* CNCM I-745 showed decreased  $\text{Ca}^{2+}$ -stimulated  $\text{Cl}^-$  secretion induced by carbachol. These inhibitory effects on  $\text{Cl}^-$  secretion have been reproduced with bacterial toxin: For example in the case of CT or LT-toxin produce by Enterotoxigenic *E. coli*, which induces secretory diarrhea





**Figure 6 Scanning electron microscopy image showing *Saccharomyces boulardii* CNCM I-745 and *Saccharomyces typhimurium* on a monolayer of T84 polarized cells. A and B: Electron microscopy image showing *Saccharomyces typhimurium* adhesion to *Saccharomyces boulardii* CNCM I-745; C and D: Confocal microscopy images showing *S. typhimurium* (Fluorescein IsoThioCyanate labelling), which adheres to *S. boulardii* CNCM I-745 (rhodamine labeling) *in vitro* (C) and *in vivo* on mouse cecum sections (D). Photos A and B: D. Czerucka<sup>1</sup>, P. Gounon<sup>2</sup>, P. Rampal<sup>1</sup>; C and D: D. Czerucka<sup>1</sup>, R. Pontier-Bres<sup>1</sup>, P. Rampal<sup>1</sup> (<sup>1</sup>CSM, Monaco, microscopy Platform Cote d'Azur, MICA; <sup>2</sup>University of Nice-Sophia-Antipolis). Sb: *Saccharomyces boulardii* CNCM I-745; St: *Salmonella typhimurium*.**

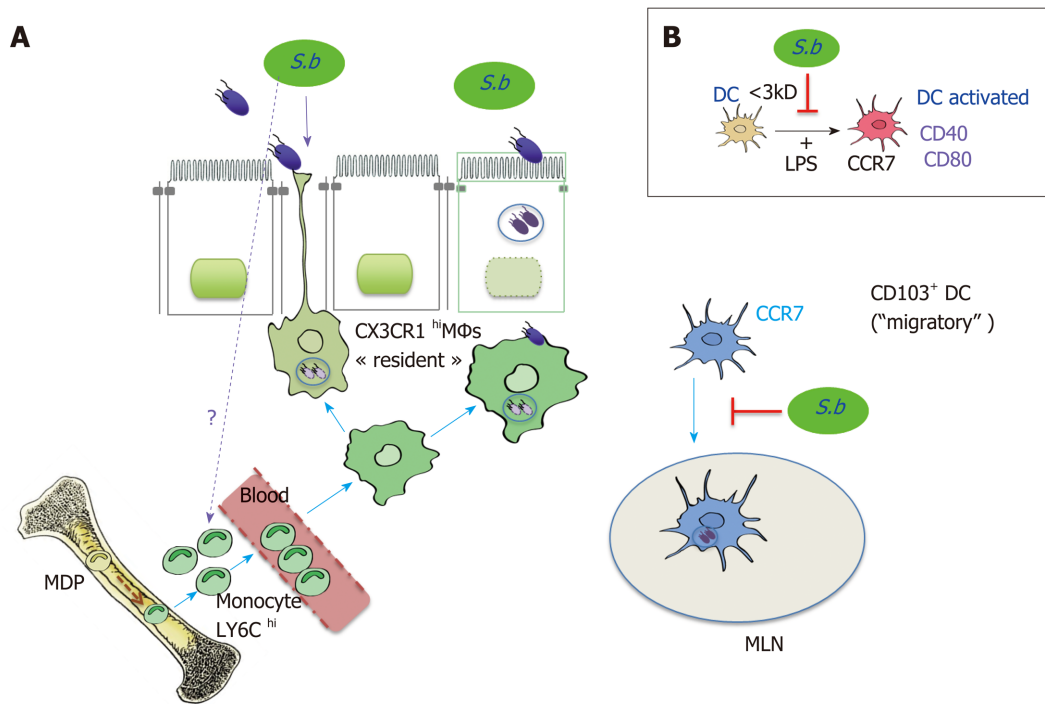
primarily by activating cAMP-activated Cl<sup>-</sup> secretion. The authors demonstrate that the culture supernatant of *S. boulardii* CNCM I-745 exerts an anti-secretory effect, suggesting the existence of a factor secreted by the yeast that could act on the cAMP dependent Cl<sup>-</sup> secretion<sup>[23]</sup>. The anti-secretory effect of *S. boulardii* CNCM I-745 on the secretion of Cl<sup>-</sup> was also suggested in a rat model exposed to prostaglandin-2<sup>[61]</sup>. However in this model, *S. boulardii* CNCM I-745 stimulates the absorption of Cl<sup>-</sup> in the jejunum and colon. *S. boulardii* CNCM I-745 exerted an antisecretory effect in other models that did not involve Cl<sup>-</sup> channels. In a rat study, prophylactic administration of *S. boulardii* CNCM I-745 showed a potent effect on castor oil-induced secretory diarrhea in a dose-dependent manner<sup>[62]</sup>. This effect is significantly inhibited by L-arginine, suggesting the involvement of the nitric oxide pathway. Finally, *S. boulardii* CNCM I-745 also has an effect on short chain fatty acid (SCFA) synthesis: Butyrate, acetate and propionate, which play a role in the absorption of water and electrolytes. Treatment with clindamycin decreases the daily production of acetate, propionate and butyrate in pigs<sup>[63]</sup>. Simultaneous administration of *S. boulardii* CNCM I-745 and the antibiotic maintains acetate and propionate at their initial levels. In another study performed on patients receiving exclusive enteral nutrition, treatment with *S. boulardii* CNCM I-745 reduced fecal SCFA concentrations to normal, particularly for butyrate<sup>[64]</sup>. This property may account in part to the anti-diarrheal and anti-inflammatory effects of *S. boulardii* CNCM I-745.

One of the roles of the intestinal epithelium is to prevent microorganisms present in the intestinal lumen from accessing the tissues. Immune exclusion is the process by which microorganisms are prevented from crossing the intestinal barrier. This is done through tight junctions that provide a mechanical barrier and the combination of mucus-containing fluid and secreted IgA that allows the sequestration of microorganisms. Finally, the intestinal immune system also plays a crucial role in eliminating pathogenic bacteria that evade immune exclusion. In previous sections of this review we saw that *S. boulardii* CNCM I-745 was able to maintain the structure of

tight junctions in monolayers of infected cells. The effect of *S. boulardii* CNCM I-745 on IgA is the subject of one of the first studies on the mechanism of action of this yeast. This study showed that *S. boulardii* CNCM I-745 induces an increase in the concentration of secretory IgA in the intestinal fluid and an increase in the secretory component of the polymeric immunoglobulin receptor in cryptic cells of the intestinal mucosa in young rats 14 d after weaning<sup>[65]</sup>. This effect appears transient, as another study done on adult rats shows that after 21 d of administration of *S. boulardii* CNCM I-745 the yeast has no effect on IgA secretion, intestinal mucosal or circulating lymphocyte populations<sup>[66]</sup>. The effect of *S. boulardii* CNCM I-745 on IgA was confirmed in *C. difficile* infections, and furthermore, administration of the yeast to mice exposed to inactivated toxin A increases the level of circulating anti-toxin A IgA<sup>[62]</sup>. More recently, *in vitro* and *in vivo* studies showed a direct action of *S. boulardii* CNCM I-745 on cells of the innate immune system (Figure 7). DC plays a key role in the balance between immunity and tolerance, and participate in the activation of lymphocytes. A recent study found that *S. boulardii* CNCM I-745 modulates the properties of DC after treatment with amoxicillin<sup>[67]</sup>. Membrane markers of antigen activity (MHC-II and CD86) are upregulated in DC of female rats treated with the antibiotic. In the presence of the yeast, these antigens are negatively regulated and the intestinal flora regains its equilibrium more quickly after stopping antibiotic treatment. This study suggests that *S. boulardii* CNCM I-745 exerts a modulatory effect on the specific immune response to microbial antigens. This has been confirmed on human DC isolated from the blood of healthy subjects exposed to LPS, which induces DC activation<sup>[68]</sup>. The authors show that a < 3 kD fraction of the culture supernatant of *S. boulardii* CNCM I-745 decreases the expression of co-stimulatory CD40 and CD80 molecules and the chemokine receptor CCR7 (a receptor that causes chemotactic migration to secondary lymphoid organs) induced by LPS. This fraction also decreases the secretion of pro-inflammatory cytokines (TNF and IL-6) and stimulates the secretion of IL-10 in DC. In addition, *S. boulardii* CNCM I-745 decreases DC-induced T cell activation<sup>[68]</sup>. In another study, the same group demonstrated that supernatant of *S. boulardii* CNCM I-745 may modify the profile of DC (CD40 and CD80 co-factors, CCR7 and cytokine profile) in the blood of patients with Crohn's Disease or ulcerative colitis<sup>[69]</sup>. In addition, this supernatant inhibits the Th1 polarization of lymphocytes and induces the secretion of IL-8 and TGF $\beta$ , two cytokines involved in the reconstitution of the epithelium. Recently our group demonstrated that in a model of Salmonella-infected mice, *S. boulardii* CNCM I-745 decreases the DC population expressing CD103<sup>+</sup> that migrate to the MLN and are responsible for the bacterial translocation to MLN. The yeast also acts on another population of macrophage which express the fractalkine receptor CX3CR1 (CX3CR1<sup>hi</sup> M $\Phi$ s) and are present in the Lamina Propria (LP). Thanks to extensions between epithelial junctions, this population of highly phagocytic cells recognize intra-luminal antigens, including pathogenic bacteria. They phagocytose them, and unlike CD103<sup>+</sup>DCs do not migrate into the MLN but are locally induced in the LP activated T lymphocytes. The population of these CX3CR1<sup>hi</sup> M $\Phi$ s in *S. boulardii* CNCM I-745-treated mice infected with Salmonella. The increase in this population comes from the expansion of circulating pro-inflammatory monocytes (mono Ly6C<sup>hi</sup>, CX3CR1<sup>int</sup>) that are recruited from the bone marrow of mice treated or not with *S. boulardii* CNCM I-745 and then infected. In the presence of the yeast, monocytes differentiate to CX3CR1<sup>hi</sup> M $\Phi$ s and their ability to phagocytose Salmonella increases significantly. These results demonstrate that *S. boulardii* CNCM I-745 can act on the immune response during the early phase of infection<sup>[70]</sup>. The CX3CR1<sup>hi</sup> M $\Phi$ s has been involved in tolerance to the microbiota. In mice with induced dysbiosis and treated with antibiotics, the population of CX3CR1<sup>hi</sup> M $\Phi$ s decreases. Administration of *S. boulardii* CNCM I-745 during antibiotic therapy increases the population of CX3CR1<sup>hi</sup> M $\Phi$ s. The impact of this increase on the reconstitution of intestinal flora remains to be demonstrated.

## EFFECTS ON THE INTESTINAL MICROBIOTA

Several studies conducted in humans and mice show that *S. boulardii* CNCM I-745 has no effect on the intestinal microbiota of healthy subjects, however, in some diseases there is an effect on intestinal dysbiosis (Table 1). In a model of amoxicillin-treated mice, antibiotic treatment increased the Enterobacteriaceae and *Bacteroides* populations and decreased *Clostridium coccooides* and *Eubacterium rectale*. Treatment with *S. boulardii* CNCM I-745 did not influence changes in the gut microbiota during antibiotic treatment but accelerated the return to normal that occurred after 10 days in these mice versus 22 d in untreated mice<sup>[67,71]</sup>. Swidsinski *et al*<sup>[72]</sup> developed an



**Figure 7 Effect of *Saccharomyces boulardii* CNCM I-745 on intestinal mononuclear phagocytes: Dendritic cells expressing CD103 (CD103<sup>+</sup>DC) and macrophage expressing the fractalkine receptor (CX3CR1MΦs).**

A. CD103<sup>+</sup>DC which expresses the CCR7 on their surface phagocytose the *Salmonella* (ST) and migrate to the mesenteric lymph nodes (MLN). CX3CR1MΦs which have a high phagocytosis capacity, include bacteria, do not migrate, but remain in the LP where they stimulate T lymphocytes. These MΦs are able to form extensions that pass between the epithelial cells and capture the antigens in the intestinal lumen, among other pathogenic bacteria such as ST. *Saccharomyces boulardii* CNCM I-745 induces the recruitment of CX3CR1MΦs and promotes phagocytosis of ST by these cells. *S. boulardii* CNCM I-745 effects the expansion of Ly6C inflammatory monocytes, which are the precursors of CX3CR1 DCs in the bone marrow. In addition, *S. boulardii* CNCM I-745 reduces the number of ST that migrate to MLN by decreasing the number of migratory DCs. B. *In vitro* studies have shown that *S. boulardii* CNCM I-745 can modify lipopolysaccharide activation of migratory DCs. This effect would be due to a molecule of low molecular weight (< 3 kDa) present in *S. boulardii* CNCM I-745 conditioned medium<sup>[64]</sup>. Sb: *Saccharomyces boulardii* CNCM I-745; ST: *Salmonella*; MLN: Mesenteric lymph nodes; DCs: Dendritic cells; LPS: Lipopolysaccharide.

innovative technique based on *in situ* hybridization (FISH) of stool samples collected by coring, which enables quantitatively assessing microbiota in the mucus, in the germinal reserve area and in the central fermentation area. This technique was used to compare and localize bacterial populations in healthy subjects and patients with idiopathic chronic diarrhea treated or not with *S. boulardii* CNCM I-745. Stools from healthy subjects are characterized by, a mucus layer of 5–60 m with homogeneous fluorescence, high concentrations of three usual bacterial groups (*Bacteroides*, *Roseburia* and *Faecalibacterium prausnitzii*) and low concentrations of occasional bacterial groups. In patients with diarrhea, the authors observed a thickening of the protective mucous layer, mucous layer incorporation in the stool, a reduced concentration of usual bacteria, an inhibition of the metabolism with appearance of areas devoid of hybridization signal and a stratification with increased levels of the occasional bacteria. Treatment with *S. boulardii* CNCM I-745 has no effect on the microbiota of healthy subjects, but the microbiological and clinical symptoms of diarrhea are reversible after treatment with the yeast. *S. boulardii* CNCM I-745 reduces the thickness of the mucus layer and increases the concentration of two usual bacterial groups: *Bacteroides* and *Roseburia*. Yeast treatment also decreases the abundance of the occasional bacterium *Akkermansia muciniphila*.

In a recent study using the same technique (coring and FISH), Swidsinski *et al.*<sup>[73]</sup> investigated the effect of *S. boulardii* CNCM I-745 on the reconstitution of intestinal flora after antibiotic treatment in patients with vaginal infection. In this study a group of patients was treated with metronidazole and ciprofloxacin, a second group received yeast during antibiotic treatment and a third group was treated with yeast after antibiotic therapy. Antibiotic treatment significantly decreased the number of bacteria in the dominant group (*Clostridium cocoides*, *Eubacterium rectum*, *Faecalibacterium prausnitzii*, *etc.*) mainly located in the fermentation zone. Treatment with *S. boulardii* CNCM I-745 during antibiotic therapy increased these populations and post-antibiotic treatment allowed these populations to return to normal. Identification of bacteria in the stool by bacterial 16S RNA sequencing confirmed that

Table 1 Effects of *Saccharomyces boulardii* CNCM I-745 on gut microbiota in various diseases

Disease	Technique	Alteration of the microbiota	Effet of <i>S.boulardii</i> CNCM I-745	Ref.
Antibiotic treatment (mice)	FISH and cytometry	Increase in Enterobacteriaceae and <i>Bacteroides</i>  Drastic decrease in <i>Clostridium cocoides</i> and <i>Eubacterium rectale</i>	Rapid return to normal for: <i>Bacteroides</i> , <i>Clostridium cocoides</i> , <i>Eubacterium rectale</i> , <i>Prevotella</i> , <i>Porphyromonas</i>	[67,71]
Chronic diarrhea (humans)	Coring and FISH	Increase in <i>Bifidobacterium</i> , <i>Eubacterium cylindroides</i> , <i>Clostridium histolyticus</i> et  Decrease in <i>Bacteroides</i> et <i>Roseburia</i>	Decrease in <i>Bacteroides</i> and <i>Roseburia</i>	[72]
Antibiotic Treatment (humans)	Sequencing	Increase in <i>Parabacteroides</i> and <i>Escherichia/Shigella</i>  Decrease in <i>Ralstonia</i>	Reduces microbiota variations due to antibiotic treatment	[74]
Antibiotic Treatment (women <sup>1</sup> )	Corning and FISH	Decrease in dominant microbiota: <i>Clostridium cocoides</i> , <i>Eubacterium rectale</i> , <i>Bacteroides</i> , <i>Roseburia</i> and <i>Faecalibacterium prausnitzii</i>	Group A/Sb: Increase in <i>Bacteroides</i> , <i>Roseburia</i> and <i>Faecalibacterium prausnitzii</i>  Groupe Sb-A: Rapid return to normal	[73]

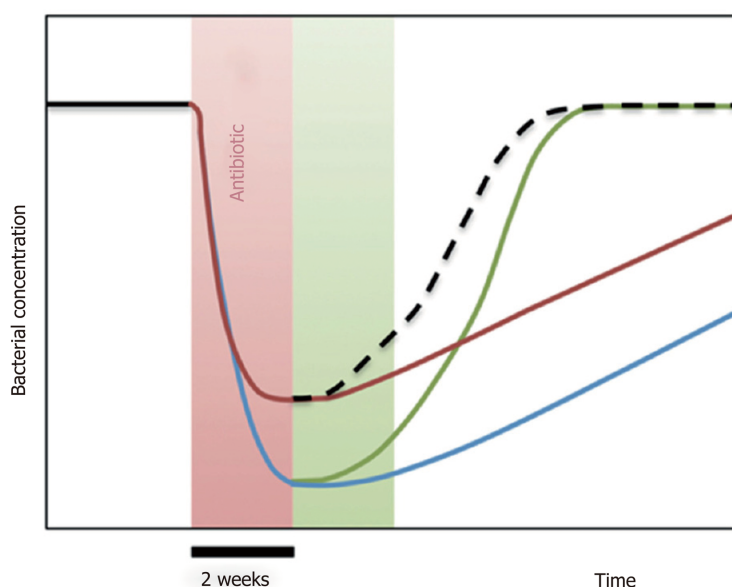
FISH: Fluorescence in situ hybridization; A/Sb: Group of patients concomitantly treated with antibiotics and *Saccharomyces boulardii* CNCM I-745; Sb-A: Group of patients treated with *Saccharomyces boulardii* CNCM I-745 after antibiotic treatment; *S.boulardii*; *Saccharomyces boulardii*.

<sup>1</sup>Patients with vaginal infections.

*S. boulardii* CNCM I-745 did not alter the microbiota composition of healthy subjects<sup>[73]</sup>. In patients treated with amoxicillin, there was a decrease in *Ralstonia* and an increase in *Parabacteroides* and *Escherichia/Shigella* in the fecal microbiota. In the group treated with *S. boulardii* CNCM I-745 and antibiotic, changes in the composition of the microbiota are significantly attenuated. A summary of the effect of *S. boulardii* CNCM I-745 on antibiotic-associated dysbiosis is presented in Figure 8. These results suggest that an optimal use of *S. boulardii* CNCM I-745 would be to administer it during and after antibiotic therapy. More and Swidsinski<sup>[75]</sup> recently published a review that summarizes all preclinical and clinical data on the effect of *S. boulardii* CNCM I-745 on intestinal microbiota associated and not associated with mucus.

## CONCLUSION

*S. boulardii* strain CNCM I-745 is a probiotic yeast that by virtue of being a eukaryote differs from other probiotic strains, which are of bacterial origin (prokaryote). The research shows a great diversity in its mode of action and types of targets: pathogens, pathogenic toxins, gut microbiota and intestinal epithelium. Two main mechanisms were demonstrated: the first one is a large capacity of the wall to fix bacteria and toxins which facilitates their elimination during intestinal transit and the second one is the synthesis by this yeast of several active factors. These factors include high molecular weight proteins, some of which have antiseptory effects, others act as proteases that degrade toxins or their receptors. Factors of small size and protein or non-protein nature that exhibit anti-secretory or anti-inflammatory activities are also involved in its action. Finally, *S. boulardii* CNCM I-745 acts on different components that maintain the intestinal barrier: Tight junctions that regulate permeability; reconstitution of the microbiota after antibiotic therapy; and, activation of innate immunity which stimulates innate defenses of the host during infection. The optimization of the use of this probiotic in infections requires a better knowledge of the different mechanisms of action.



**Figure 8** Diagram illustrating the impact of *Saccharomyces boulardii* CNCM I-745 on dysbiosis during antibiotic therapy. A 2-wk treatment with antibiotics (red zone of the graph) induces a sudden decrease in the dominant bacterial populations of the microbiota (blue curve). Treatment with *Saccharomyces boulardii* CNCM I-745 during antibiotic therapy (red curve) reduces the sudden decrease in bacterial populations. When *S. boulardii* CNCM I-745 is administered after antibiotic therapy (green zone of the graph, green curve) the yeast accelerates the restoration of the intestinal flora to its initial level. An optimal use of yeast would be administration during and after antibiotic therapy, which is presented by the hatched curve resulting from the red and green curve (from reference<sup>[75]</sup>).

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