The probiotic *Saccharomyces boulardii* upgrades intestinal digestive functions by several mechanisms

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Abbreviations : BBM : Brush Border Membrane ; *S. boulardii* : *Saccharomyces boulardii* ; MAP kinase : Mitogen activating kinase ; ERK_1 – ERK_2 Extra membrane signal regulating kinase 1,2 ; $SGLT_1$: Sodium glucose cotransporter –1.

To the Editor,

S*accharomyces boulardii* (*S. boulardii*) is a probiotic yeast largely prescribed in many countries over the world. This probiotic has shown to exhibit therapeutic properties in acute and chronic enterocolopathies, irritable bowel syndrome, antibiotic – associated – diarrhoea and enterotoxigenic *Clostridium difficile* infections (1) However, the mechanisms of its effects remain largely unknown. The aim of this letter is to propose three complementary mechanisms explaining its trophic effects. In human volunteers (2) and growing rats (2), oral administration of lyophilized preparations of *S. boulardii* produces trophic intestinal effects including increases in the specific and total activities of sucrase and maltase-glucoamylase in epithelial cells and in endoluminal fluid, enhanced secretion of s-IgA in intestinal fluid (3) and enhanced synthesis of the secretory component (receptor for polymeric immunoglobulins) in crypt cells (3). Also, rats treated with lyophilized preparations of *S. boulardii* show a marked stimulation of the sodium – dependent D-glucose uptake with a corresponding increase in the sodium D-glucose co-transporter 1 ($SGLT_1$) (4). Recently we demonstrated that yeast cells can release in the endoluminal compartment a sucrase proteine (2, 6), a leucine aminopeptidase acting as a zinc-binding metalloprotease (6) and a novel protein phosphatase that inhibits *Escherichia coli* endotoxin by dephosphorylation (7). Stimulation of microvillous enzymes by *S. boulardii* was confirmed in human enterocytes by an in situ histochemistry method (8). Since *S. boulardii* secretes a great amount of sucrase, totalizing more than 8000 units per g of lyophilized preparation (2), yeast cells are used to treat children with congenital sucrase-isomaltase deficiency (9). In addition, lyophilized *S. boulardii* is recognized by OMS authorities as an effective treatment for *Clostridium difficile* overgrowth (1).

To complete the digestion of sugars, *S. boulardii* delivers an α,α-trehalase in the intestinal lumen of rats which could be efficient to treat trehalose intolerance (10). Expressed per gram of powder, α,α-trehalase from *S. boulardii* delivered in vitro an activity 175 times higher than the activity of human trehalase expressed per gram of intestinal mucosa (10).

Like as with sucrase, the luminal secretion of an α-amylase (11) acting on starch α, 1-4 bounds and of a maltase-glucoamylase (2,11) acting on the last glucosyl-unit of each amylopectin chain could implicate oral treatment of *S. boulardii* in the digestion and metabolic degradation of starch.

Beside the secretion of enzymes and of nutrient carriers in the intestinal lumen, the stimulation of brush border membrane enzymes and of carriers is at least in part mediated by the endoluminal release of polyamines (12) meanly spermine and spermidine. Lyophilised preparation of yeasts contain significant quantities of polyamines, totalling 679 nanomoles/100mg of lyophilised preparation meanly spermidine (55%) and spermine (43%) with negligible amounts of putrescine (1.4%). In theory, such amounts of polyamines could influence intestinal expression of brush border membrane glycoproteins (hydrolases, proteases and transport molecules). In practice, a marked stimulation of disaccharidases and aminopeptidase activities and of the secretion of secretory IgA has been observed in the small intestine of young unweaned rats in response to oral ingestion of spermine and spermidine, equivalent to 1000 nanomoles/day of purified polyamines (12). When infant rats were given an amount of spermine (500 nanomoles/day) equivalent to the polyamine content of the lyophilised preparation of yeast cells (679 nanomoles/100 mg) similar enzymatic responses were observed, including significant increases in the specific and total activities of sucrase (× 2,5) and maltase

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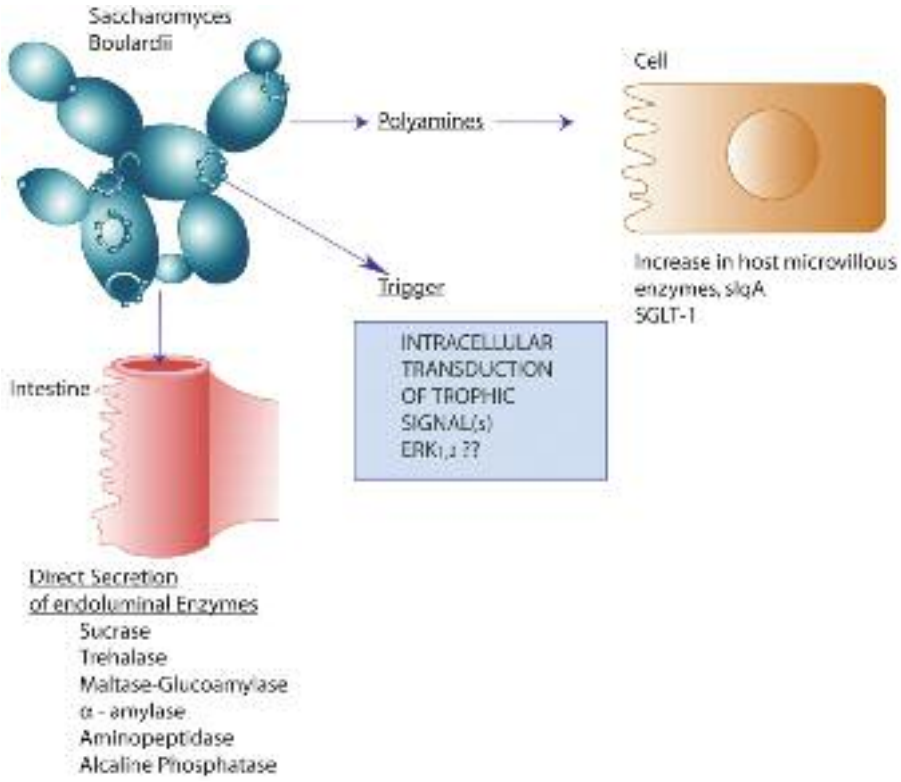

Fig. 1. — The Figure represents the three mechanisms of action of the probiotic *Saccharomyces boulardii*

(+ 24%). In response to 1000 nanomoles of spermine, enzyme stimulation was proportionally greater with increases in sucrase (× 4,6) and maltase (+ 70%) activities. Similarly, weaned rats treated with either *S. boulardii* or equivalent quantities of spermine (500 nanomoles) presented parallel, significant increases in specific sucrase (157%) and maltase (+ 47,5%) activities. Therefore, oral administration of 100 mg lyophilised *S. boulardii* containing 679 nanomoles of polyamines to breast fed sucklings reproduced similar changes in microvillous enzymes than the administration of 500 nanomoles of spermine. Regarding the stimulation of microvillous enzymes, the oral administration of spermine is a dose – dependent phenomenon. It is more sensitive for sucrase than for other microvillous enzymes (lactase, aminopeptidase, maltase-glucoamylase) and becomes detectable at doses of spermine as low as 250 nanomoles/day. After absorption, polyamines act at the level of DNA synthesis, mRNA expression and protein production. Lastly, recent experiments indicate that *S. boulardii* inhibits the signal transduction triggered by *E. coli* on in vitro intestinal cell lines, essentially interleukin 8 ad NF-kB (13).

Up to now, the precise mechanism by which yeast cells triggers signals transduced in epithelial cells remains unknown. However, the ERK_1 and ERK_2 MAP kinases could be involved because these messengers are activated at the epithelial cell membrane by trophic signals and transduce them into the cell to the nucleus (14, 15). Furthermore, the disacharidase activities are inhibited by specific ERK inhibitors (14). Further studies are warranted to determine the nature of the signal(s) transduced into epithelial cells.

In conclusion : oral administration of lyophilised *S. boulardii* upgrades intestinal functions meanly by three mechanisms : 1) the endoluminal secretion of enzyme proteins by the yeast itself ; 2) the endoluminal secretion of polyamines (spermine and spermidine) that after absorption enhances the synthesis of BBM proteins, enzymes and carriers ; and 3) the possible intracellular activation of messengers which transduce trophic signals from the apical membrane to the nucleus.

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