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REVIEW

Twenty-Five Years of Research on *Saccharomyces boulardii* Trophic Effects: Updates and Perspectives

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Commentaries

Saccharomyces boulardii (*S. boulardii*) was discovered by Henri Boulard in 1920 in Indochina. Since then, lyophilized preparations of *S. boulardii* have increasingly been used throughout the world, providing empirical evidence of its efficacy as an adjuvant agent to treat diarrhea and prevent antibiotic-associated complications. Since 1982, the year of the first publication [1], increasing numbers of studies have been conducted each year to determine the mechanism(s) of action of *S. boulardii* and to evaluate whether it has beneficial properties for the host organism. More recently, placebo-controlled, double-blind studies have demonstrated the efficacy of *S. boulardii* as a probiotic medication and as a biotherapeutic agent in some intestinal disorders in both children and adults. The target intestinal disorders are listen in Table 1 along with the corresponding references [2–28]. The references listed here were selected from the MEDLINE database (NIH, National Library) from among 247 publications, including both clinical and experimental studies. The number of publications on *S. boulardii* has increased since the mid-1990s, now reaching 15 publications per year, while very recently meta-analyses have demonstrated the beneficial effects of *S. boulardii* treatment, mainly in *Clostridium difficile*-associated disease, antibiotic-associated diarrheas, and acute infectious diarrheas.

Saccharomyces boulardii is a nonpathogenic yeast widely prescribed in a lyophilized form in many countries of the world and used as a biotherapeutical agent [30–32]. The objective of the present report is to provide an update on the intestinal trophic properties of *S. boulardii* in endoluminal fluid and in intestinal cells at a molecular level. Several authors, using different methods of molecular biology, have shown [33–35] that *S. boulardii* strains are clustered within the species of *S. cerevisiae*, the latter having no probiotic effect. The taxonomic position of *S. boulardii* was evaluated by sequence analysis of the D_1/D_2 domain of 26S rDNA, the ITS1-5.8S rDNA-ITS2 region, and the mitochondrial cytochrome-c oxidase II gene [36].

The trophic effects of *S. boulardii* on human and on rat small-intestinal cells have been studied since 1986 [37] and show that oral administration of the lyophilized preparation of the yeast results in a stimulation of human and rat brush border membrane (BBM) enzymes including lactase, sucrase-isomaltase, maltase glucoamylase [37], and α,α-trehalase. Incorporation of ^{14}C-glucosamine into lactase precursor was stimulated by *S. boulardii* cells whether cells were viable or killed by heating [37]. In addition, oral therapy enhanced the intestinal synthesis of the receptor for polymeric immunoglobulins and the secretion of s-IgA [38] and transporters such as the sodium–glucose cotransporter $SGLT_1$ with increase in glucose uptake by BBM vesicles [39]. Although the precise mechanisms by which yeast cells exert these trophic effects remain unknown there are at least three potential explanations. First, orally given yeast cells secrete directly into the endoluminal fluid enzymes such as sucrase, α,α-trehalase, aminopeptidase [40], and a phosphatase that dephosphorylates very actively the endotoxin of *E. coli* 55B5, resulting in an inactivation of the toxins by more than 60% as attested by the marked reduction in tissue TNF-α levels and in the absence of liver and cardiac tissue lesions [41].

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Table 1 Clinical intestinal disorders for which *S. boulardii* treatment has been shown to exert beneficial effects

Disorder	References
Diarrheas	
Antibiotic-associated diarrhea	[2–4]
Acute infectious	[5, 6]
Amebiasis	[7]
Acute and subacute giardiasis	[8]
Clostridium difficile enterocolopathies	[9–11]
Pseudomembranous enterocolitis	[12]
Traveler's diarrhea	[13, 14]
Acute *Helicobacter pylori*	[15, 16]
Chronic persistent diarrhea	[9, 17]
Chronic protracted diarrhea	[9]
AIDS-associated diarrhea	[18]
IBD	
Crohn's disease	[19]
Ulcerative colitis	[20]
Continuous enteral feeding	[21]
Critically ill tube-fed patients	[22]
Hirschsprung's disease, enterocolitis	[23]
Pediatric age group	[9, 24–26]
Prematures	[27]
Infants, children	[24–26]
Autism and diarrhea	[28]
Irritable bowel	[29]

Secondly, we have demonstrated that yeast cells contain significant amounts of polyamines (678 nmol/100 mg), mainly spermidine (376 ± 32 nmol/100 mg) and spermine (293 ± 26 nmol/100 mg), which are released in the small intestine and are absorbed by semi-active transport and stimulate enzymes expression, protein synthesis, and DNA replication [42]. These observations led us to suggest that the trophic effects of *S. boulardii* are mediated at least in part by the endoluminal release of spermine and spermidine. This hypothesis warrants further studies since oral spermine can increase sucrase mRNA [43] and affect intestinal [43] and liver maturation [44].

Thirdly, mature rat intestinal cells contain all the molecules involved in the transduction of extramembranous signals for growth and maturation, such as extracellular regulated kinases 1 and 2 (ERK_1 and ERK_2), phospholipase c-isoenzyme gamma (PLC-gamma), phosphotidyl inositol-3 kinase (Pi-3 kinase), the Ras-GTPase-activating protein (GAP) associated with RhO-GAP and p62 (SRc), protein kinase B (PKB), protein kinase C (PKC) Src homology 2 alpha-collagen protein, (SHC) GLUT 4, GLUT 5, p38 mitogen-activating protein (MAP) kinases, NFkB, and caspases [45]. Inhibition of PI-3 kinase by wortmannin in rats stimulated in a dose-dependent fashion the expression of sucrase protein and sucrase activity. This can only be explained by cross talk between the PI-3 kinase pathway and the ERK_1 and ERK_2 pathway, which could have been stimulated by the inhibition of PI-3 kinase [45, 46].

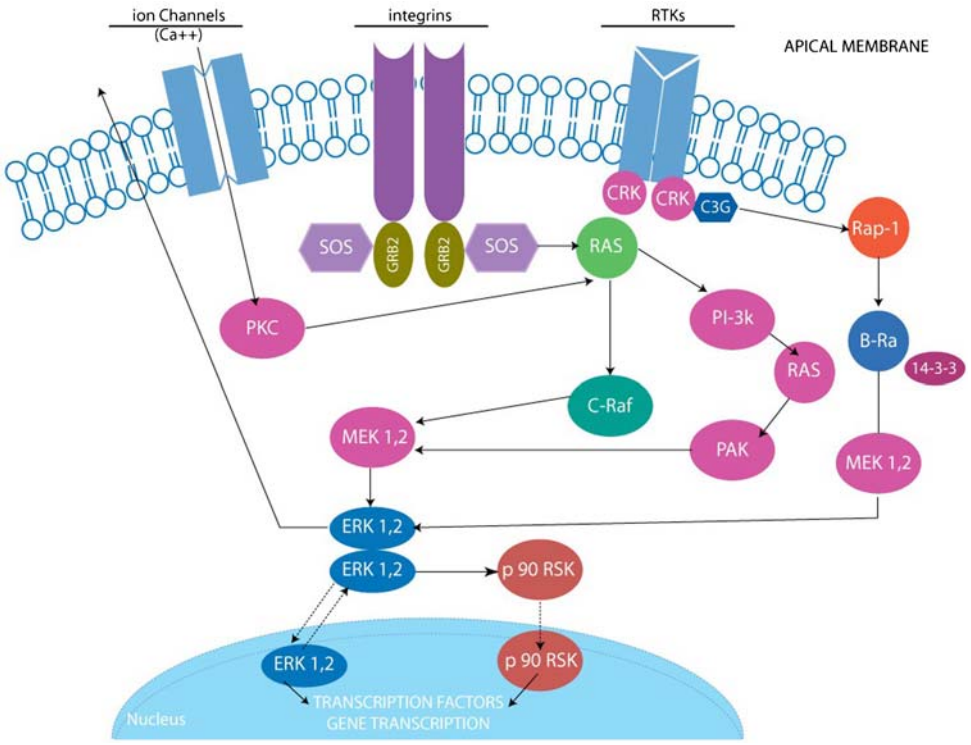

Fig. 1 Transduction of intracellular signals for cell growth and differentiation

Since *S. boulardii* given orally is a shuttle delivering several substances to the endoluminal compartment, it becomes of major importance to elucidate the molecular pathways stimulated by the yeast and their metabolic or physiological effects in the host. Beside the molecular transduction pathways of insulin, IgF-1, and other trophic peptides, the MAPK/ERK_{1-2} cascades and the PI-3 kinase signaling pathway represent two molecular transduction pathways of major interest for the understanding of how the yeast cell works (Fig. 1). The MAPK/ERK signaling cascade can be activated by a wide variety of receptors involved in growth and differentiation, including receptor tyrosine kinase (RTks), integrin receptors, and ion channels. The specific components of the cascade vary greatly among different stimuli, but the architecture of the pathway usually includes a set of adaptor molecules (ShC, GRb_2, PLCgamma, CRK) linking the receptor to a guanine nucleotide exchange factor (SOS, PKC, C3G). This transduces the signal to small GTP binding proteins (Ras, RapS, C-Raf), which in turn activate the core unit of the cascade composed of MAPKKK (Rap), MAPKK (MEK 1, 2), and MAPK 1, 2 (ERK_1, ERK_2). An activated ERK dimmer can regulate targets in the cytosol and translocate to the nucleus, where it phosphorylates a variety of transcription factors regulating gene expression [47, 48].

The transcription factors that regulate gene expression include c.FOS, STAT 1 and 3, CREB, PAX6, c-MYC, TIF 1A, and Ets. Alternately, G-protein-coupled receptors are also activated by a wide variety of external stimuli (proteins of the yeast?). Upon receptor activation, the G-protein exchanges a guanidine diphosphate (GDP) for a guanidine triphosphate (GTP), causing the dissociation of the GTP-bound alpha and beta/gamma subunits and triggering diverse signaling cascades. Receptors coupled to different heterotrimeric G-proteins subtypes can utilize different scaffolds to activate the small G protein/MAPK cascade, employing at least three different classes of tyrosine kinases. SRC family kinases are recruited following activation of PI-3 kinase gamma by beta/gamma subunits. They are also recruited by receptor internalization, signaling through an integrin scaffold, or employ PLC beta to mediate PKC and CaMK II (casein MAP kinase II), which can have either stimulatory or inhibitory consequence for the downstream MAPK pathway [49].

Conclusion

The trophic effects exerted by the probiotic *S. boulardii* on human and animal intestinal tract are mediated by direct (and/or indirect) stimulations linked to the endoluminal release of several substances (enzymes, proteins, lipids, polyamines, etc.). The mechanism(s) of cell stimulation or the receptor(s) involved are unknown but the end step of the cellular stimulations could be the MAPkinase cascade with phosphorylation through intranuclear ERK_1 and ERK_2 of transcription factors initiating gene expression. Beside the microvillous uptake of endoluminal polyamines released by the yeast, the factor(s) from the yeast that initiate the trophic effects remain largely unknown and warrant further investigation to document the properties of this biotherapeutic agent.

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