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Coevolution of yeast mannan digestion: Convergence of the civilized human diet, distal gut microbiome, and host immunity

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The complex carbohydrates accessible to the distal gut microbiota (DGM) are key drivers in determining the structure of this ecosystem. Typically, plant cell wall polysaccharides and recalcitrant starch (i.e. dietary fiber), in addition to host glycans are considered the primary nutrients for the DGM; however, we recently demonstrated that α-mannans, highly branched polysaccharides that decorate the surface of yeast, are also nutrients for several members of *Bacteroides* spp. This relationship suggests that the advent of yeast in contemporary food technologies and the colonization of the intestine by endogenous fungi have roles in microbiome structure and function. Here we discuss the process of yeast mannan metabolism, and the intersection between various sources of intestinal fungi and their roles in recognition by the host innate immune system.

Keywords: catabolism, carbohydrate active enzyme, distal gut microbiota, evolution, fungal cell wall, mannooligosaccharide, polysaccharide, symbiosis, yeast mannan

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Background

Domesticated yeast has transformed the quality and festivity of mealtimes for thousands of years. Antiquated texts put the dawn of yeast applications in human food and drink production around 3,000–5,000 BC; some evidence however, suggests that they likely originated earlier in the Neolithic era.[1] Recently, we discovered that yeast mannan, a cell wall carbohydrate of *Saccharomyces cerevisae* (i.e., baker's yeast; **Fig. 1**) and other fungi, is specifically metabolised by several members of the distal gut microbiota (DGM).[2] The term mannan was derived from 'manna' (Hebrew: מן) – the flaky sweet substance that the Israelites consumed during their exodus in the desert (Numbers 11:1–9); similarly, yeast mannan today still clearly contributes to the nutrition of the DGM as the genes required for its degradation are still broadly represented in the gut metagenomes of healthy human subjects. Yeast mannan defines the outermost boundary between the fungus and its environment, and is involved in a number of physiological events related to fungal cell wall stability and remodeling.[3] Fungal carbohydrates also define key elements for host immune recognition and defense (**Fig. 1**;[4,5]).

The 'sugar-coated' surface of yeast

Yeast mannan is synthesized onto a $GlcNAc_2$-$Man_{8–9}$ acceptor, a highly conserved core oligosaccharide in eukaryotic glycoproteins, in the Golgi apparatus by a series of specific glycosyl transferases.[6] The first steps involve the M-Pol I complex, which contains 2 family 62 glycosyl transferases Mnn9p and Van1p.[7,8] Mnn9p catalyzes the first reaction and primes $Man_8GlcNAc_2$ with a single α-1,6 decoration, which is then extended into a highly conserved α-1,6-mannan backbone, comprising ~200 Man units, by Van1p. This backbone is decorated by species-specific sidechains. For example, *S. cerevisiae* sidechains contain Man-α-1,3→Man-α-1,2→Man-α-1,2→Man with occasional phosphomannoligosaccharide branches; whereas the invasive pathogen *Candida albicans* displays Man-β-1,2 oligosaccharides of varying length that cap the α-linked Man side chains (**Fig. 1**). These terminal structures represent 2 of the growing list of signature carbohydrate structures that are being linked to fungal perception and host immunity.[5]

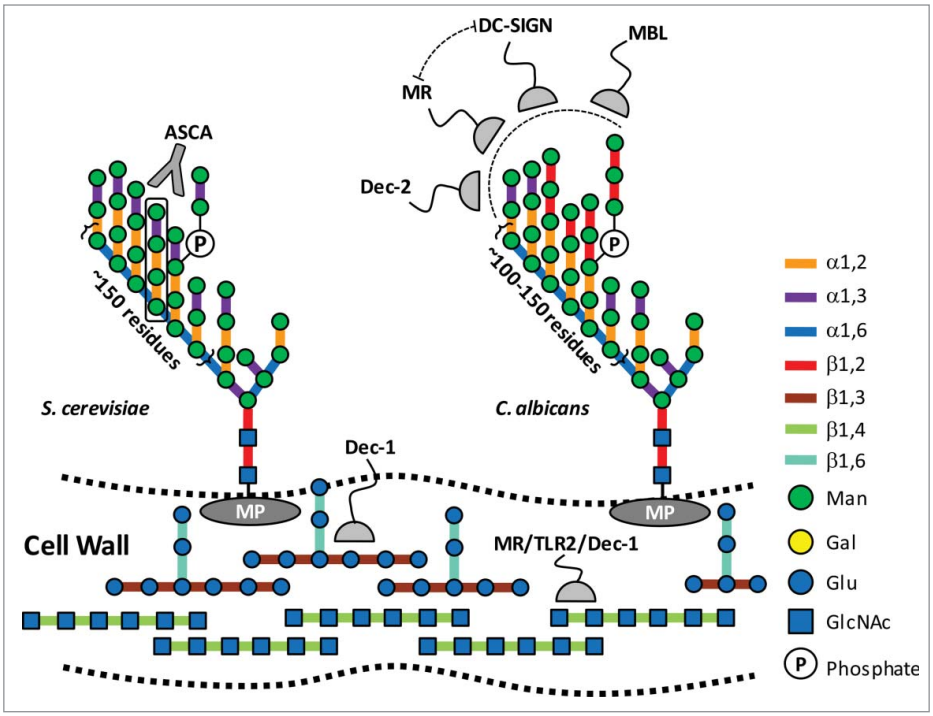

Figure 1. Structures of immunogenic carbohydrates within fungal cell walls. The composition of the cell wall of yeast and filamentous fungi varies between species; however, there are structural similarities. These include chitin (β-1,4-N-acetylglucosamine) and β-1,3(β-1,6)-glucans, which are core elements that provide tensile strength to the cell wall; and surface mannoproteins (MP). Yeast mannan is a highly branched complex carbohydrate an α-1,6 backbone, with α-1,2; and α-1,3-linked mannose sidechains. Some sidechains are further branched though phosphate ester bonds. *C. albicans* mannan has a conserved core structure with *S. cerevisiae*, but displays signature β-1,2 mannosyl residues at the termini of its sidechains. Numerous host immune responses to these polysaccharides have been documented,[4,5] and several examples are displayed here. β-Glucans and chitin are important targets because they represent conserved elements across a spectrum of fungal species. Dectin-1 (Dec-1) is a C-type lectin receptor with high affinity for pure β-1,6 branched β-1,3 glucans.[34] Immune responses to chitin are complex and yet to be fully elucidated, but they have been shown to involve macrophage mannose receptor, TLR2, and Dec-1.[27] α-Mannans represent the outermost feature of the fungus, and have been linked to a variety of innate and adaptive responses. The mannotetraose (Man-α1,3→Man-α1,2→α-1,2→Man) sidechains of *S. cerevisiae* are antigens for ASCA, an antibody which is found in higher titres in individuals with CD (black box;[32]). Several proteins are known to interact with *C. albicans* mannans, including the C-type lectin receptor dectin-2 (Dec-2); mannose binding lectin (MBL);[28] and MR[29] and dendritic cell receptor (DC-SIGN),[30] which have combinatorial effects.

Orchestrated metabolism of yeast mannan by the DGM

The human genome contains only a handful of CAZymes known to be active on dietary carbohydrates, and the majority of those are involved in the digestion of α-glucans (e.g. isomaltooligosaccharides, starch) and sucrose within the upper alimentary canal.[9] The vast bulk of dietary polysaccharides are impervious to human digestion and they transit to the colon where they are depolymerized and fermented into short chain fatty acids by the DGM, which are subsequently utilized by the host. One of the hallmark features of the DGM is the prevalence of bacteria such as *Bacteroides* spp whose genomes encode a large number of carbohydrate active enzymes (CAZymes) dedicated to the metabolism of dietary fiber.[10] The colon is a highly competitive microbial ecosystem with diverse species competing for limited nutrients. In order to persist, intestinal residents occupy select niches or adapt successful metabolic strategies. One such strategy has been exploited by the Bacteroidetes, which has many members that operate as nutritional 'generalists'.[11,12] Generalists harness catabolic machinery targeting a wide variety of complex carbohydrates, the major nutrient available to the DGM. Thus the extensive repertoire of CAZymes enable the organisms of the DGM to respond to the variation in available dietary nutrients. To optimize efficiency and limit metabolic cost, *Bacteroides* spp. organize their carbohydrate metabolic pathways into Polysaccharide Utilization Loci (PULs).[13] PULs are independently regulated functional units. Each targets a specific glycan. SusC/D-like proteins (named after the starch utilization system, the first characterized glycan degrading system in Bacteroides) function as outer-membrane bound protein complexes that recruit carbohydrates at the cell surface and facilitate transport in a predicted TonB activated process. Other features of PULs include regulatory proteins that sense the presence of a targeted substrate and activate expression of a pathway consisting of depolymerising enzymes, which release oligosaccharides and monosaccharides from polysaccharide substrates. Investigating the molecular basis of how CAZymes from *Bacteroides* spp dismantle structurally complex dietary carbohydrates has become a highly-successful strategy for enzyme discovery.

Similar to the metabolism of dietary glycans such as fructans,[14] xylan[15,16] and xyloglucan,[17] *B. theta* contains PULs that are dedicated for yeast mannan metabolism; however, it is a more complex process and represents an exception to the 'one PUL for one substrate' paradigm.[13] Three PULs (MAN-PUL1/2/3) are induced by yeast mannan, and a fourth PUL (HMNG-PUL) that targets structurally related high mannose N-glycans is induced by $Man_8GlcNAc_2$. Using a series of biochemical approaches and targeted gene disruption, we were able to define the function of the majority of genes products encoded within MAN-PUL1/2/3 (**Table 1**). These enzymes work interdependently to completely saccharify yeast mannan in a process that initiates on the cell surface and culminates with intracellular mannose. Intriguingly, MAN-PUL1 and MAN-PUL2 display a high level of synteny; however, only MAN-PUL2 is

Table 1. MAN-PUL1/2/3 gene products involved in yeast mannan metabolism

Gene	Family	Location[1]	Actvity[2]	Gene	Family	Location[1]	Actvity[2]
PUL-Man1				PUL-Man2			
BT2620	GH97	P	exo-α-galactosidase	BT3773	GH92	P	exo-α-1,3 mannosidase[3]
BT2621	ORF	C	unknown	BT3774	GH38	P	exo-α-mannosidase
BT2622	GH67	C	unknown	BT3775	GT32	C	α-1,3 glycosyl transferase
BT2623	GH76	E	endo-α-1,6 mannanase	BT3776	GT32	C	α-1,6 glycosyl transferase
BT2624	ORF	E	unknown	BT3777	ORF	P	unknown
BT2625	SusD-like	E	transport	BT3778	ORF	C	unknown
BT2626	SusC-like	OM	transport	BT3779	ORF	C	unknown
BT2627	ORF	E	unknown	BT3780	GH130	P	unknown
BT2628	HTCS	IM	regulator	BT3781	GH125	P	exo-α-1,6 mannosidase
BT2629	GH92	P	exo-α-1,3 mannosidase	BT3782	GH76	P	endo-α-1,6 mannanase
BT2630	PTase	P	mannose-6-P phosphatase	BT3783	PTase	P	mannose-6-P phosphatase
BT2631	GH76	P	endo-α-1,6 mannanase	BT3784	GH92	P	exo-α-1,2 mannosidase[3]
BT2632	GH125	P	exo-α-1,6 mannosidase	BT3785	ORF	C	unknown
PUL-Man3				BT3786	HTCS	IM	regulator
BT3853	SARP/OmpR	IM	regulator	BT3787	ORF	E	unknown
BT3854	SusC-like	OM	transport	BT3788	SusC-like	OM	transport
BT3855	SusD-like	E	transport	BT3789	SusD-like	E	transport
BT3856	ORF	E	unknown	BT3790	ORF	E	unknown
BT3857	ORF	C	unknown	BT3791	SGBP	E	unknown
BT3858	GH92	P	exo-α-1,3 mannosidase[3]	BT3792	GH76	E	endo-α-1,6 mannanase
BT3859	ORF	E	unknown				
BT3860	ORF	E	SGBP				
BT3861	ORF	E	SGBP				
BT3862	GH99	E	endo-α-1,2 mannosidase				

[1]Locations are predicted using the LipoP 1.0 tool[35] or inferred using biochemical data. C = cytoplasm; IM = inner membrane; P = periplasm; OM = outer membrane; E = extracellular surface.
[2]Activities have been validated experimentally.
[3]Reported in.[36] SGBP = surface glycan binding protein.

indispensable, suggesting that there is functional specialization that has co-evolved within these pathways. This is exemplified by the capacity of the mannan PULs to accommodate diverse sugars and/or linkages found in other fungal species, such as *Candida albicans*[18] and *Schizosaccharomyces pombe*.[19] These findings suggest that high-mannose containing complex carbohydrates are valuable nutrients for *B. theta* proliferation or it exposes an important role for the symbiotic turnover of fungal carbohydrates in the intestine; 2 roles that may not be mutually exclusive. Indeed, there is a strong selective pressure for yeast mannan degradation and its significance for host health may extend beyond nutrient acquisition. Thus, while MAN-PULs are activated in the mammalian host, deletion of these genetic loci confers a significant advantage over the wild type bacterium in diets lacking the yeast glycan, and this metabolic trait is very highly conserved in different strains of *B. theta.*

Mannan utilization is a selfish process

Depolymerisation of yeast mannan is metabolically expensive. The complex, highly branched substrate greatly restricts enzyme access and its degradation requires a large number of enzymes (**Table 1**). In the metabolism of other complex carbohydrates, some organisms simplify transport by centralizing depolymerisation outside of the cell. For example, the 'cellulosome' is a large multienzyme complex found within some members of Clostridia that often tethers an extensive repertoire of plant cell wall degrading glycanases on the cell surface (**Fig. 2**). Extracellular processing comes at cost, however, as simple sugars released from complex substrates by 'keystone species' become accessible to other local residents.[20] In these scenarios, carbohydrate metabolism is a 'shared' process and individuals can occupy ecological niches along catabolic cascades by specializing in stratified levels of carbohydrate or metabolite utilization.[16,21] The model of yeast mannan metabolism by *B. theta* represents a 'selfish' alternative to this theme as limited processing occurs outside of the cell (**Fig. 2**). Complex mannooligosaccharides are generated by first exposing and cleaving the α-1,6 mannan backbone at sparse sites and then shuttling these branched fragments across the outer membrane. Importantly, the extracellular enzymes that cleave the backbone operate at noticeably slower rates than their counterparts within the periplasm. This ensures that fragments are produced at a rate that will not saturate the transport equilibrium, which would result in loss of excess products to the environment.

Co-culturing experiments with *B. theta* and *Bacteroides xylanisolvens* and *Bacteroides cellulosilyticus*, 2 species that cannot metabolize yeast mannan but can grow on mannose, support this selfish model.[2] When provided with only yeast mannan as a carbon source, *B. theta* growth rates are unperturbed in co-culture whereas both of its relatives do not exhibit significant growth. This finding underpins that

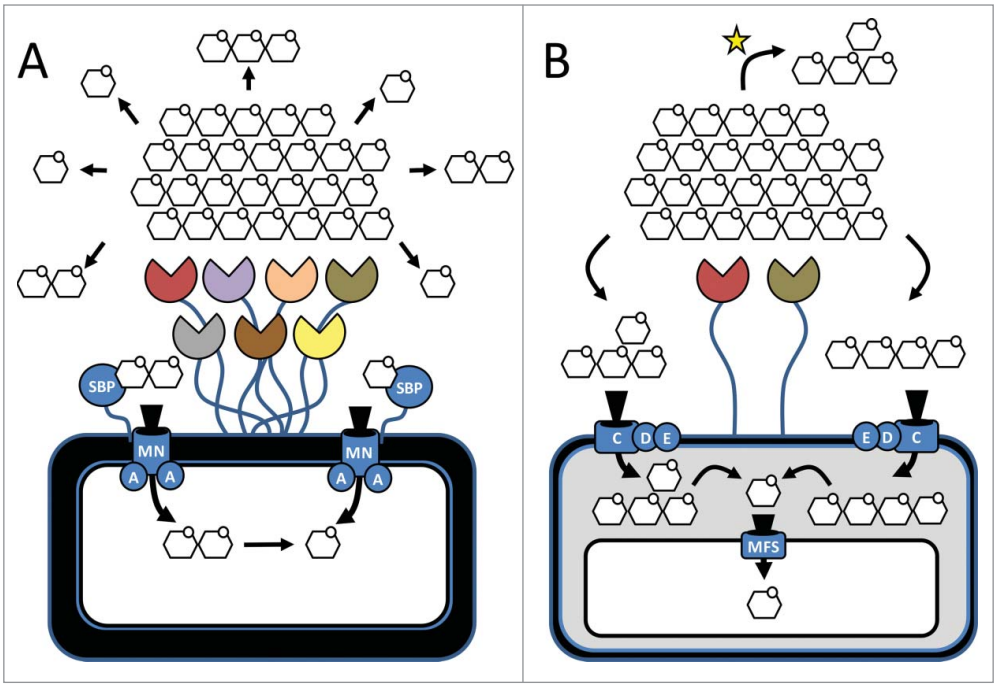

Figure 2. Strategies for extracellular digestion of complex carbohydrates. (**A**) The 'sharing'-strategy: extracellular enzymes or enzyme complexes (e.g., Cellulosomes) process complex carbohydrate substrates into simple sugars and small oligosaccharides. These substrates can be readily utilized by any proximal bacterium. In Gram (+) bacteria products are bound by solute binding proteins (SBPs) and transported across the cell wall by ATP-dependent transporters MNA_2. (**B**) The 'selfish'-strategy: minimal extracellular processing of the substrate. Complex oligosaccharides are transported into the periplasm through the Sus-like transport system where the bulk of depolymerisation occurs. Monosaccharides enter the cytoplasm through a major facilitator superfamily (MFS) transporter. Variations of this pathway exist as come complex oligosaccharides released during extracellular processing may be selectively used by other bacteria in the ecosystem (indicated with a yellow star); however, they remain inaccessible to the majority of bacteria within proximity.

B. theta deploys a selfish mode of yeast mannan metabolism and prevents the superfluous release of mannose or mannooligosaccharides into the media to be shared with other species. Significantly, this relationship may be substrate specific, and one needs to be cautious before extrapolating whether *B. theta* is solely selfish in its metabolism, as a selective sharing relationship was recently demonstrated between *Bacteroides ovatus* and *Bifidobacterium adolescentis*[16], and several members of Bacteroidales with differing growth aptitudes were able to liberate oligosaccharides (i.e. "public goods") from multiple carbohydrate sources into solution for utilization by other species ([21]; **Fig. 2**). The tendency of PULs to concentrate complex oligosaccharide depolymerising enzymes within the periplasm,[14,17,22,23] however, suggests that *B. theta* is primarily concerned with self-nourishment and symbioses with other species may be dependent on the chemistry or complexity of the substrate.

A coupled catabolic-biosynthetic cascade to reprofile exogenous mannose?

MAN-PUL2 contains the first characterized example of coupled mannan catabolism and mannooligosaccharide biosynthesis in nature. A putative biosynthetic cassette contains 2 intracellular family 32 glycosyl transferases (GT32s; BT3775 and BT3776;) that sequentially catalyze the synthesis of a branched α-mannose trisaccharide that is likely decorated further by other biosynthetic components encoded within MAN-PUL2 or inherent capsular polysaccharide synthesis pathways. To ensure that nascent α-Man_3 products are not indiscriminately digested the catabolic and anabolic stages of mannose processing are compartmentalized into the periplasm and cytoplasm, respectively.

Although the downstream role of α-Man_3 remains to be resolved, it is likely either a component of a storage molecule or a capsular polysaccharide. The typansomatid protozoan *Leishmania* spp. synthesizes an intracellular β-1,2 mannan that is harvested when glucose becomes limiting,[24] and bacterial glycogen (i.e., α-1,4 (α-1,6)-glucan) is a storage reserve in over 40 different bacterial species.[25] Alternatively, α-Man_3 may be incorporated into the capsule of *B. theta*. A previous study determined that disrupting Bt3775 or genes encoding the capsular polysaccharide 4 (CPS4) biosynthetic pathway removed a surface epitope recognized by 225.4, an IgA monoclonal antibody raised in a germ-free mouse colonized with *B. theta*.[26] The potential interplay between yeast mannan metabolism, α-mannooligosaccharide synthesis, and capsular remodeling represents a unique response of *B. theta* to dietary yeast and warrants further investigation.

Fungal immune perception and *B. theta*

Chitin (β-1,4-N-acetylglucosamine) and β-1,3(β-1,6)-glucans are the primary structural polysaccharides of the fungal cell wall. These repetitive structures are not found within human glycans, and therefore, make ideal targets for the recognition of foreign symbionts or opportunistic pathogens (**Fig. 1**). In this regard, the perception of fungal polysaccharides has been linked to numerous innate and adaptive immune responses involving surveillance proteins, such as dectin-1 (Dec-1), mannose receptor (MR), and toll-like receptor 2 (TLR2).[4,5,27] Yeast mannan on the other hand shares compositional and stereochemical similarity with human high mannose N-glycans; although, it is substantially larger and its sidechains are capped with Man-α-1,3-Man instead of Man-α-1,2-Man (**Fig. 1**). In addition, carbohydrate heterogeneity within fungal

mannans, such as the β1,2 mannosyl caps that decorate the surface of the opportunistic pathogen *Candida albicans*, are structural signatures that can be detected by other immune sentinel proteins, such as the C-type lectin receptor dectin-2 (Dec-2); mannose binding lectin (MBL);[28] and MR[29] and dendritic cell receptor (DC-SIGN),[30] a process which can involve combinatorial interactions (**Fig. 1**).

The sidechains of yeast mannan have been linked to perturbed immune responses in patients with Crohn's disease (CD), a debilitating inflammatory autoimmune disorder that presents in the small bowel and colon. Anti-*S. cerevisiae* antibodies (ASCA) preferentially recognize the sidechain structure of yeast mannan (Man-α-1,3→Man-α-1,2→Man-α-1,2→Man),[31] and have been found in higher titres in the sera of CD patients. Intriguingly, the DGM of CD patients has a marked reduction in the abundance of *B. theta* in comparison with healthy individuals (∼35%).[32] Additionally, higher levels of *Bacteroides* spp have been associated with CD patients in remission when compared to those that have relapsed.[33] It is tempting to speculate that this relationship may result, at least in part, from a reduced ability of a compromised DGM (i.e. lacking *B. theta*) to tolerate and digest mannans from dietary or endogenous yeasts.

In culture *B. theta* PUL-MAN expression is high within its carbohydrate metabolism hierarchy, and these pathways are actively expressed *in vivo*,[2] underpinning the importance of yeast mannan responsive enzymes. For example, BT3862 is an extracellular endo-α-1,2-mannosidase from MAN-PUL3 that prunes yeast mannan sidechains by specifically cleaving within the ASCA epitope and releasing Man-α-1,2→Man[2] Exploiting this relationship may have therapeutic potential for alleviating ASCA-associated exacerbations and *B. theta* has received orphan drug status by the FDA for the treatment of pediatric CD. In this light, harnessing the mechanistic roles of naturally occurring members of the DGM for improving intestinal health and developing applications for offsetting dysbioses that result from improper regulation of DGM community structure is a promising research avenue for next generation 'live-culture' biologics.

Conclusion

The analysis of yeast mannan degradation by *B. theta* provides a model for the depolymerisation and utilization of complex sterically constrained carbohydrates by *Bacteroides*. The bacterium has evolved a surface enzyme system that is optimized to produce a large number of oligosaccharides for import into the periplasm where depolymerisation is completed. This mechanism minimises the energy used in the import process and the loss of nutrients to the environment, and thus represents a selective advantage for the bacterium. While this cellular deployment pattern of enzyme systems is conserved for other glycans, the discriminating factor between selfish and sharing metabolism appears to be substrate dependent. Extracellular digestion of 'accessible' glycans (i.e., sterically unconstrained) results in the release of oligosaccharides into the environment where they become available to other organisms in the DGM.[16,21]

Both the sources of yeast mannan molecules and the significance of their turnover by the DGM for host health may extend beyond nutrient acquisition. For example, recent efforts have been aimed at defining and enumerating the fungal members of the microbiota ("mycobiome") during health and disease and it is possible that *B. theta* has evolved to utilize mannans from a variety of endogenous yeasts that colonize the gut. In addition, while cultural consumption of foods that are fermented with yeast is a uniquely human endeavor, yeasts are naturally present in a variety of foods such as ripe and spoiled fruits and may therefore have impacted microbiota evolution in other animals as well. Regardless of the source, it should be emphasized that there is apparently a strong selective pressure for yeast mannan degradation in *B. theta*. This evidence emanates from our observation that these 3 PULs are consistently activated in the mammalian host even in the absence of usable mannan, perhaps in response to an inducing signal derived from endogenous N-glycans or another source that mimics the presence of the yeast polysaccharide. Surprisingly, deletion of these loci in *B. theta* conveys a substantial competitive advantage over the wild type bacterium in diets lacking the yeast glycan, while wild-type bacteria compete best when bona fide mannan is present as a nutrient. Thus, while deployment of this 'expensive' metabolic trait decreases the fitness of *B. theta*, it has remained highly present in nearly all strains of this species that were analyzed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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