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Mannoside recognition and degradation by bacteria

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ABSTRACT

Mannosides constitute a vast group of glycans widely distributed in nature. Produced by almost all organisms, these carbohydrates are involved in numerous cellular processes, such as cell structuration, protein maturation and signalling, mediation of protein–protein interactions and cell recognition. The ubiquitous presence of mannosides in the environment means they are a reliable source of carbon and energy for bacteria, which have developed complex strategies to harvest them. This review focuses on the various mannosides that can be found in nature and details their structure. It underlines their involvement in cellular interactions and finally describes the latest discoveries regarding the catalytic machinery and metabolic pathways that bacteria have developed to metabolize them.

Key words: mannosides, mannans, N-glycans, carbohydrate active enzymes.

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I. INTRODUCTION

Mannose is one of the simplest and common hexoses found in nature. As a monomer, it can be used by most living organisms to support their growth. When integrated into glycans, it can also be used as an energy source, signalling

molecule, or cell-structuring element, especially in plants. Mannosides thus play a key role in metabolism and cell recognition, and are involved in many diseases, often linked to protein glycosylation disorders (Sharma, Ichikawa & Freeze, 2014). Life has evolved many kinds of mannosides with different functions, and the appropriate processes to

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synthesize them. Many bacteria have also developed different or complementary strategies to detect and degrade these compounds. In addition, as mannosides are involved in cell signalling, mannosylated proteins take part in the detection of pathogens. While several previous reviews consider mannoside degradation, this review provides a general overview of the occurrence of mannosides produced by living organisms, their involvement in cell–cell interactions, and the most up-to-date insights on mannoside assimilation by bacteria living in different environments, mainly focusing on β -mannans and N-glycans. A detailed description of the known mannoside structures will introduce this review.

II. DIVERSITY OF MANNOSIDE STRUCTURES

(1) Eukaryotic mannosides

Mammals, plants, yeasts and fungi have a wide array of mannosides, either in the form of pure glycans or as glycoconjugates. The latter refers to mannosyl residues carried by proteins as post-translational modifications, to those linked to lipids, or to hybrid structures containing proteic, lipid and glycan components. In glycoproteins, mannosyl residues are mostly found in N-linked glycans, although O-linked glycans and glycosylphosphatidylinositol (GPI) anchors also contain mannosyl residues. With the exception of hemicelluloses which are specific to plants, other mannosides are produced by all eukaryotes. The mechanisms used for their biosynthesis are similar between different taxa, but inter-specific variations exist both in their structure and synthesis pathways.

(a) Mammalian mannosides

N-glycans are the most common form of mannosides found in mammals (Apweiler, Hermjakob & Sharon, 1999). These glycans are attached to asparagine (N) residues of the majority of proteins, shaping their properties (Skropeta, 2009). N-glycan biosynthesis has been detailed previously in several reviews (Helenius & Aebi, 2004; Aebi *et al.*, 2010; Larkin & Imperiali, 2011), and will not be considered here. The N-glycan maturation processes yields different N-glycan structures, depending on the fate of the protein, but all mature N-glycans share a common $\text{Man}_3\text{GlcNAc}_2$ pentasaccharide core. Addition of N-acetylglucosaminyl, galactosyl, fucosyl or sialyl residues yields a wide array of structures that can be grouped under three different classes: high mannose (HMNGs), complex (CNGs) and hybrid N-glycans (HNGs) (Fig. 1A). Mammalian N-glycans found on mature proteins are rarely of the HMNG class, but are rather hybrid or complex, HMNG being mostly restricted to immature proteins (Nagae & Yamaguchi, 2012).

O-mannosyl glycans are a second form of mannosides bound to mammalian proteins (Lommel & Strahl, 2009). Previously believed to be restricted to fungi, where they are highly abundant (De Groot, Ram & Klis, 2005), they have also been identified in metazoans and particularly

in humans where they occur mainly in nerve tissues or chondroitin sulfate proteoglycans (Praisman & Wells, 2014). Similar to N-glycans, O-mannosyl glycans display relatively broad structural diversity. All, however, share a common β -D-GlcNAc-(1 \rightarrow 2)-D-Man core structure which can be extended by additional sugars (galactosyl, sialyl, glucuronyl, N-acetylglucosaminyl or fucosyl residues), that are species specific (Fig. 2A).

GPI anchors are post-translational modifications of the C-terminal region of many proteins, allowing them to bind to the outer layer of the cell membrane (Paulick & Bertozzi, 2008). A large number of GPI-anchored proteins have been identified in eukaryotes, ranging from protozoa and fungi to humans. A GPI anchor structure is formed by three domains: a phospholipid tail, a conserved glycan region and a phosphoethanolamine moiety linked to the bound protein (Ikezawa, 2002). The glycan region is formed of a highly conserved α -D-Man β -(1 \rightarrow 2)- α -D-Man β -(1 \rightarrow 6)- α -D-Man β -1,4- α -D-GlcNAc-1,6-*myo*-inositol motif (Fig. 2C). This core can be extensively modified by attachment of side chains containing phosphoethanolaminyl, mannosyl, galactosyl, sialyl, N-acetylglucosaminyl and N-acetylgalactosaminyl residues (Fujita & Kinoshita, 2010). GPI anchors are found in a wide array of proteins involved in signal transduction (Mukasa *et al.*, 1995), immunity, interaction with trypanosomal parasites (Ferguson *et al.*, 1988), or even prion pathogenesis (Chesebro *et al.*, 2005).

C-mannosylation is a much rarer event. It has been observed in mammals, mostly humans, and other animals (Furmanek & Hofsteenge, 2000; Munte *et al.*, 2008; Buettner *et al.*, 2013), but not in plants, yeast, fungi or prokaryotes. It consists of the formation of a α -C–C bond between a mannosyl moiety and the C₂ atom of the indolyl moiety of tryptophan, on the first tryptophan of the conserved motif W-x-x-W (Löffler *et al.*, 1996). Literature on this topic is very scarce, but this modification seems to be present in proteins involved in immunity, such as complement proteins (Hofsteenge *et al.*, 1999) or interleukin-12 (Doucey *et al.*, 1999). Its role is still unclear, but recent studies indicate its involvement in secretion (Goto *et al.*, 2014) and activity tuning, since the secreted Cys subdomains of Muc5A/C and Muc5B lung mucin protein have been found to be retained in the endoplasmic reticulum (ER) if unmannosylated (Perez-Vilar, Randell & Boucher, 2004). C-mannosylation has also been observed in viruses. The Ebola viral protein sGP, which is the first reported example of viral C-mannosylation, seems to be unaffected by this post-translational modification, as no significant change in expression, folding or activity was observed relative to the unmannosylated state (Falzarano *et al.*, 2007). Further investigations are necessary to elucidate the specific roles of this type of glycosylation, its biosynthesis regulation, and how this very uncommon glycan linkage is degraded, particularly by bacteria.

(b) Plant mannosides

With the exception of O- and C-mannosides, plant mannosides have similar mannosides to mammals. However,

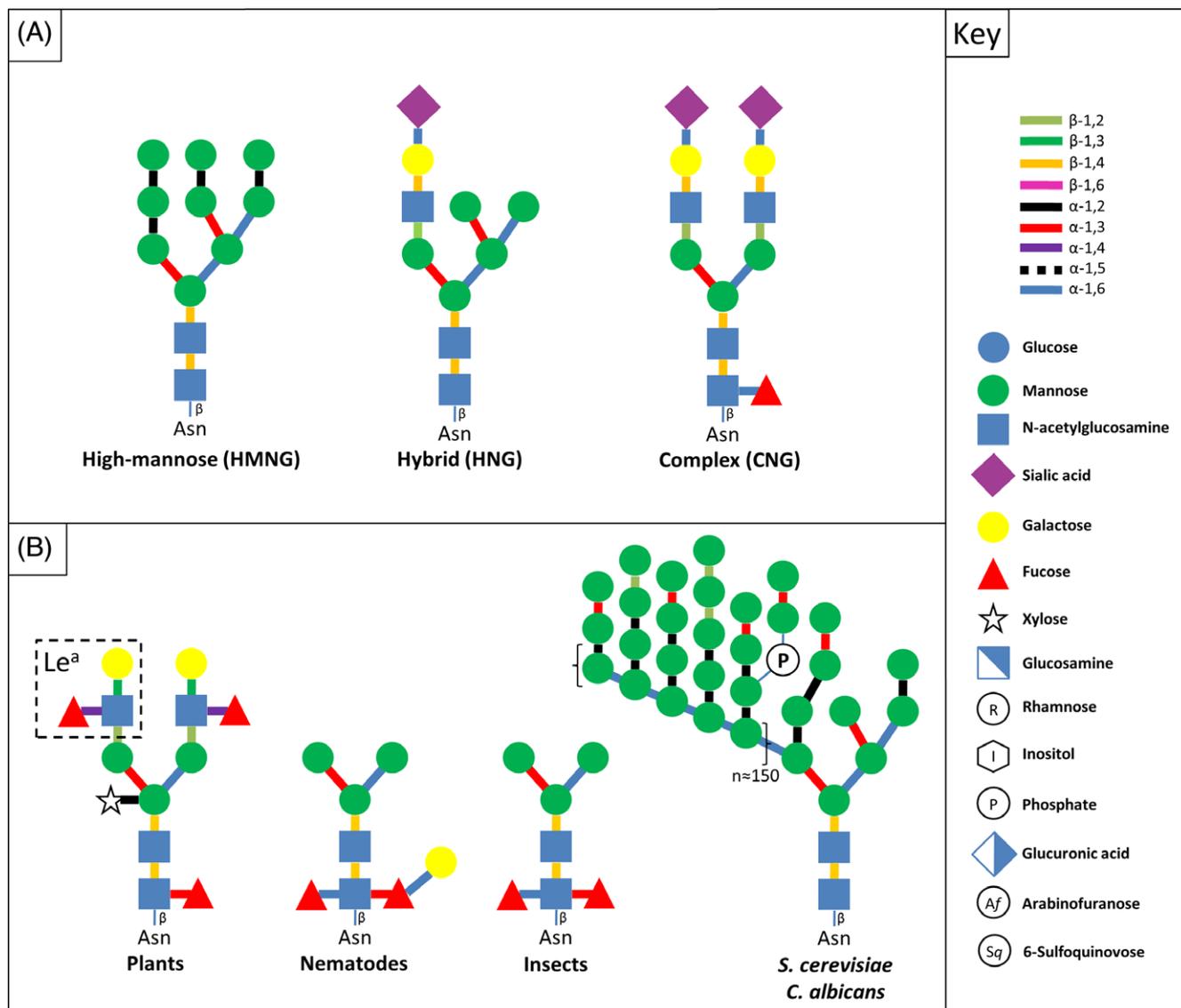


Fig. 1. Eukaryotic N-glycan structures. (A) Structure of the three classes of mature N-glycans. (B) Typical structures of mature N-glycans found in various eukaryotic organisms. The Lewis antigen (Le^a), Fuc- α -(1 \rightarrow 4)-[Gal- β -(1 \rightarrow 3)]-Glc p Nac trisaccharide often found on plant or food allergens is highlighted. Note that the very high mannose type N-glycan present in yeasts is similar between *S. cerevisiae* and *C. albicans*, with minor variations. *S. cerevisiae* lacks the β -1,2 linked mannosyl residues and contains a long α -1,6 branch which is about 150 residues long, compared to the 100–150 residues branch found in *C. albicans*.

there are some structural differences and plants also possess specific mannosyl-containing molecules, hemicellulosic β -linked mannans, that are found elsewhere.

The first steps in plant N-glycan synthesis are identical to those in mammals, and also rely on the formation of the Glc₃Man₉GlcNac₂ precursor in the ER (Pattison & Amtmann, 2009; Gomord *et al.*, 2010; Song *et al.*, 2011). In addition to the ubiquitous N-x-S/T sequon used for protein attachment, an unusual N-x-C sequence has also been described (Matsui *et al.*, 2011). The maturation process again occurs in the Golgi's apparatus, but plant N-glycans display specific structural features. For instance, β -1,2-xylosyl residues linked to the β -1,4-mannosyl residue of the core

pentasaccharide, and α -1,3-fucosyl ones linked to the reducing end N-acetylglucosamine are typically found. The Lewis a epitope [Gal p - β -(1 \rightarrow 3)-[Fuc p - α -(1 \rightarrow 4)]-Glc p Nac] is also found at the extremities of plant CNG branches (Fig. 1B). This epitope, found on what is called 'secreted type N-glycan', has been found in many foodstuffs (Wilson *et al.*, 2001) and pollen allergens (Maeda *et al.*, 2005). In plants, protists, archaea, eubacteria and fungi, β -1,4-linked galactosyl and sialyl residues, which are the signature of mammalian complex N-glycans, are absent (Zeleny *et al.*, 2006). However, the unicellular green algae *Chlamydomonas reinhardtii* CC-125 produces mammalian-like N-glycans, containing both the β -1,4-Gal and the sialylated complex

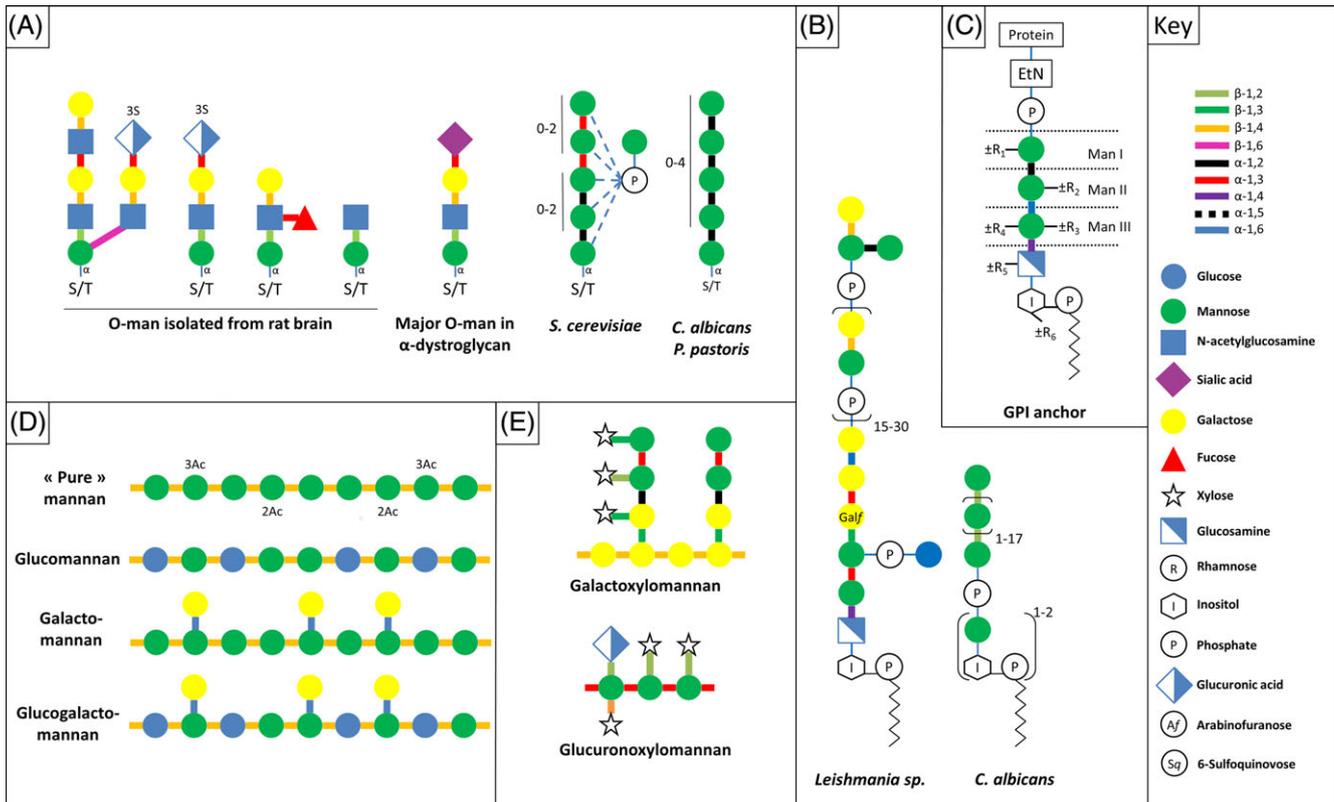


Fig. 2. Structures of other eukaryotic mannosides. (A) Structure of eukaryotic O-mannans. (B) Typical structures of lipophosphoglycans. *Galf*, galactofuranose. (C) Highly conserved structure of the glycosylphosphatidylinositol (GPI) anchor found in all eukaryotes. EtN, ethanolamine. (D) Structures of plant mannans, with examples of each subclass. (E) Structures of fungal capsular polysaccharides.

glycan structure together with a plant-like core α -1,3 fucosylation (Mamedov & Yusibov, 2011). The so-called ‘truncated’ type N-glycan Man₃-Xyl-GlcNAc₂-Fuc (also called paucimannose or vacuolar N-glycan) is the most commonly found type of N-glycan in vacuolar storage proteins in seeds (Kimura & Matsuo, 2000). Contrary to mammalian N-glycans, plants often carry HMNG, in some cases exclusively. For instance, algae such as *Codium fragile*, *Chondrus ocellatus*, *Sargassum piluliferum* or *Zostera marina* contain only HMNGs, being devoid of CNGs (Yoshiie *et al.*, 2012). Contrary to mammals, for which CNG defects are almost associated with diseases (congenital disorders of glycosylation), N-glycan processing in plant Golgi may be dispensable, although it is associated with disease under certain stress conditions (Strasser, 2014). In plants, free forms of N-glycans have also been detected at micromolar concentrations, during all stages of development (Maeda & Kimura, 2014). They originate mostly from misfolded protein processing, but they have also been found ubiquitously in plant tissues associated with auxin-like function, participating for instance in stem elongation and maturation of fruits, suggesting a specific role for these molecules (Meli *et al.*, 2010).

GPI-anchored proteins are also found in plants (Borner *et al.*, 2003). They are involved in many biological functions,

such as cell surface synthesis and remodelling (Liu *et al.*, 2013) or pollen tube–female gametophyte interactions (Capron *et al.*, 2008). They are structurally very similar to those of animals or yeasts (Schultz *et al.*, 1998). However, the presence of a galactosyl residue linked to the β -1,4 mannosyl of the core pentasaccharide seems to be plant specific (Ellis *et al.*, 2010).

In plant cell walls, cellulose microfibrils are associated with a dense network of hemicelluloses, pectins, structural glycoproteins and lignin. The different proportions of these polymers show high variation among species, tissues and developmental stages. Hemicelluloses form approximately one third of the total mass of the plant cell wall (Pauly *et al.*, 2013), and consist of heteroxylans, mixed-linkage glucans, and mannans, all containing β -linked backbones. Mannans are the most abundant hemicellulosic component of softwoods, with a widespread distribution in plant tissues. They are also found in some algae (Domozych *et al.*, 2012). Mannans can be linear or ramified. The main chain is more than 90% β -1,4-linked mannopyranosyl units in linear mannan (or pure mannan), or may contain β -1,4-linked glucopyranosyl units in various amounts in glucomannan. Galactomannan and glucogalactomannan are ramified forms bearing additional α -1,6-linked galactopyranosyl units (Scheller & Ulvskov, 2010) (Fig. 2D). More rarely (e.g. species

of Orchidaceae) 2- and 3-*O*-acetylated forms of mannans (acetylmannan) are found. Glucomannan is the major component of softwoods, with a degree of polymerization (DP) of 200 and a Man:Glc ratio of 3:1. It is less abundant in hardwoods, constituting 3–5% of cell wall, also being shorter (DP = 70) and with a Man:Glc ratio from 1.5:1 to 2:1 (Hongshu, Jinggan & Yan, 2002). Galactomannans are mainly found in endospermic tissue of seeds of Leguminosae, with roles in plant cell wall structuration and energy storage [as cell wall storage polysaccharides (CWSPs)] (Buckeridge, 2010). The abundance of galactomannans in Leguminosae, which constitute a significant part of the human diet, makes them important dietary fibres. In plants, galactomannans were also described as signalling molecules for growth and development (Liepman *et al.*, 2007). The rheological properties of galactomannan are different to those of the other mannans. The presence of galactosyl residues results in higher hydrophilic behaviour, making galactomannans useful in water retention in order to avoid seed drying (Ferreira *et al.*, 2009).

(c) Yeast and fungal mannosides

Yeasts and fungi produce essentially the same kinds of mannosides as other eukaryotes, with the exception of hemicelluloses, which are specific to plants, and C-mannosides, which have been identified only in multicellular organisms.

The vast majority of yeast and fungal glycoconjugates contain substantially larger amounts of mannosyl units compared to those of other eukaryotes. Yeasts and fungi are devoid of complex N-glycans. N-glycan precursor synthesis in the ER is highly conserved in all eukaryotes, but trimming steps in the Golgi's apparatus do vary, producing huge structures in yeast and fungi with so many mannosyl units that they are named mannan (or sometimes mannoproteins) (Munro, 2001; Hall & Gow, 2013) (Fig. 1B). Structurally, this N-glycan is close to the HMNG type found in other eukaryotes. The main difference resides in the presence of a long Man β - α -1,6-linked side chain on the central α -1,3 bisecting branch of the core pentasaccharide, which serves as a scaffold for Man β - α -1-2 ramifications. These ramifications are then capped by additional α -1,3-linked mannosyl residues. In addition, these glycans harbour branches linked through a phosphoester linkage (explaining why these N-glycosylated proteins are sometimes called phosphopeptidomannans) which can be released by acidic treatment, forming the acid-labile part of the glycan.

A specific feature of fungal N-glycans compared to yeasts is the presence of β -1,2-linked mannosyl residues on the α -1,2-linked ramifications (Shibata *et al.*, 2003). Moreover, an additional N-acetylglucosaminyl residue α -1,4 bound to the β -1,4-linked mannosyl of the core pentasaccharide has been reported in the fruiting body of the basidiomycete *Coprinopsis cinerea* strain AmutBmut (Buser *et al.*, 2010). This observation indicates that the substitution on this mannosyl is taxon dependent: plants add β -xylose, animals add β -Glc β NAc, and fungi add α -Glc β NAc. Moreover, the

N-glycans of the opportunistic pathogen *Aspergillus fumigatus* D141 harbour Gal β residues. This galactose-containing glycan (termed galactomannan) forms up to 14% of the extracellular matrix (Schmalhorst *et al.*, 2008), and has been implicated in *A. fumigatus* virulence, similarly to the *Leishmania* lipophosphoglycan detailed in Section II.1d (Loussert *et al.*, 2010). Fucosylated oligomannose N-glycans have been reported in several species belonging to the phylum Basidiomycota, indicating that fucosylation seems to be a common feature of fungal N-glycans (Grass *et al.*, 2011). The long α -1,6 side chain of fungal N-glycans seems to be shorter than that in yeast or even absent, since that of the pathogenic yeast *C. albicans* is 100–150 mannosyl residues long, compared to the 150 residue-long one found in *S. cerevisiae* (Masuoka, 2004). Finally, fungal N-glycans are long, and more similar to those in yeast when in a budding, unicellular form, while vegetative mycelium forms harbour mainly HMNGs, closer to those in other eukaryotes (Buser *et al.*, 2010).

O-mannosylation is present in most yeast and fungi, and both taxa share common structural features that differentiate them from other eukaryotes. The O-mannosides of yeast and fungi are less complex than their animal counterparts (Hall & Gow, 2013). They are almost exclusively composed of mannosyl residues, forming a chain of α -1,2- and α -1,3-linked residues of polymerization degree ranging from 1 to 5. However, other sugars such as galactopyranose, galactofuranose and glucopyranose can be present in the main chain or in ramifications, especially in filamentous fungi (Goto, 2007). In *S. cerevisiae*, a phosphomannosyl residue can be added to any of the mannosyl residues forming the main chain (Fig. 2A).

Synthesis of GPI-anchored proteins has been shown to be essential for *S. cerevisiae* survival and growth (Fujita & Jigami, 2008). The GPI moiety contains either a diacylglycerol with a very long saturated fatty acid at the sn-2 position (Fankhauser *et al.*, 1993), or a ceramide, more precisely a phytosphingosine with a C_{26:0} fatty acid, or a phytosphingosine containing a monohydroxylated C_{26:0} (Conzelmann *et al.*, 1992). Lipid remodelling steps are intimately related to lipid raft association in biological membranes, thus directly participating in activity tuning (Wang *et al.*, 2013). Regarding the glycan part of the GPI anchor, in *S. cerevisiae*, it mostly contains mannosyl residues α -1,2 or α -1,3 linked to the ManI, but the presence of phosphoethanolaminyl residues on the other branching points is variable, and appears to be absent in mature proteins (Fujita & Jigami, 2008) (Fig. 2C). *C. albicans* is thought to possess twice the number of GPI-anchored proteins of *S. cerevisiae* (Richard & Plaine, 2007). GPI anchors are essentially identical to those of other eukaryotes, and their biosynthesis follows the same pathway. However, compared to other eukaryotes, in yeasts and fungi, some mature GPI-anchored proteins can undergo an additional maturation step. The GPI anchor may be cleaved off the protein, between the glucosamine and the first mannosyl moiety, in order to direct it to the cell wall, and covalently attach it to the β -1,6

glucan (Van Der Vaart *et al.*, 1996). A specific signal in the propeptide of the nascent protein seems to be required to retain the GPI-anchored protein to the plasma membrane; those which do not possess it are directed to the cell wall (Frieman & Cormack, 2003). This signal is composed of two basic amino acids in the four amino acids upstream of the ω -site of propeptide cleavage in yeast, while in fungi this signal is composed of a single basic amino acid at the ω -1 or ω -2 sites (Ouyang *et al.*, 2013).

Fungi also possess a cell wall containing diverse polysaccharides. Among them, phospholipomannan (PLM) is a glycoconjugate first described in *C. albicans* (Trinel *et al.*, 2002) (Fig. 2B). Its glycan part is formed by a linear chain of 3–20 β -1,2-linked mannosyl residues, depending on the serotype. The lipid part is formed by a phytoceramide associating a C₁₈/C₂₀ phytosphingosine and a C₂₆, or C₂₄ hydroxy fatty acids, similarly to GPI anchors. The linker region between the lipid and the glycan part is unusual, composed of a Man β - α -1-P-6-O-Man β - α -(1 \rightarrow 2)-inositol-1-P-lipid [M(IP)] motif, or a repeated version, containing two inositol phosphate residues [M(IP)₂] (Trinel *et al.*, 2005).

Some pathogenic fungi also contain a capsule, composed from a variety of polysaccharides. It is mainly formed by association of glucuronoxylomannan (GXM) and galactoxylomannan (GalXM) (Zaragoza *et al.*, 2009) (Fig. 2E). In the pathogenic fungus *Cryptococcus neoformans*, GXM forms a long polysaccharide of 1.7×10^6 Da that comprises more than 90% of the capsule's polysaccharide mass, and mediates multiple deleterious effects on the host's immune function (Zaragoza *et al.*, 2009). GXM is composed of a α -1,3-mannan chain, which is branched by additional β -1,2 glucuronic acid residues every three mannosyl units. Depending on the serotype, additional β -1,2 or β -1,4 xylosyl residues can be added, and mannosyl residues may be 6-O-acetylated (Cherniak & Sundstrom, 1994). GalXM is much shorter (1.0×10^5 Da), and constitutes 5–8% of the capsular mass. It is formed by an α -1,6-galactan backbone to which four potential short oligosaccharide branches can be added. These branches consist of an α -(1 \rightarrow 3)-D-Man β - α -(1 \rightarrow 4)-D-Man β - α -(1 \rightarrow 4)-D-Gal β trisaccharide, which holds variable amounts of β -1,2 or β -1,3 xylosyl residues.

(d) Protozoan mannosides

In some protozoans, and particularly in *Leishmania* parasites, a particular class of mannosides is found in the glycocalyx. This molecule shares structural similarities both with the GPI anchor and the bacterial lipopolysaccharide (LPS) (see Section II.2). This structure is known as lipophosphoglycan (LPG) (Beverley & Turco, 1998). Both LPG and LPS are intimately involved in host–pathogen interactions (Kawai & Akira, 2011; de Assis *et al.*, 2012). LPS has the appearance of a GPI anchor since it is composed of a lipid tail allowing anchorage in the membrane bilayer, a phosphoinositol linker and a glycan moiety. However, in contrast to GPI anchors, the glycan part is much larger, and does not contain

a protein (Fig. 2B). LPG molecules have four parts: (i) a lipid tail (monoalkyl-lysophosphatidylinositol with saturated C₂₂–C₂₄ alkyl groups in *Leishmania* species), (ii) a core heptasaccharide, containing galactosyl, glucosyl- α -1-phosphate (linked to galactosyl residues through phosphoester bonds), mannosyl and glucosaminyl moieties, (iii) a central multiple repeated β -D-Gal β -(1 \rightarrow 4)-D-Man β -phosphate disaccharide (15–30 repeats), and (iv) a Gal β - β -(1 \rightarrow 4)-[Man- α -(1 \rightarrow 2)]-Man β - α -1-phosphate cap. This molecule plays a key role in parasite invasion and survival, mostly through the presence of a galactofuranosyl unit in the heptasaccharide core (Oppenheimer, Valenciano & Sobrado, 2011). The Gal β - β -(1 \rightarrow 4)-Man β - α -1-phosphate disaccharide also participates in antigenicity, and can be directly linked to GPI-anchored proteins involved in Trypanosomatidae-mediated diseases (Descoteaux & Turco, 1999).

(2) Prokaryotic mannosides

For a long time, bacteria and archaea were considered to be devoid of post-translational modifications other than phosphorylation. Recently, however, N- and O-glycans have been found in many bacteria and archaea (Lommel & Strahl, 2009; Calo, Kaminski & Eichler, 2010; Nothaft & Szymanski, 2010, 2013; Larkin & Imperiali, 2011). However, N- and O-glycans of prokaryotic origin differ from those of eukaryotes, since prokaryotes lack both the ER and the Golgi apparatus, the sites of assembly and maturation in eukaryotes.

Many bacterial N-glycans have been reported, but their structures mostly remain incompletely elucidated, and to date, no bacterial N-glycan structure containing mannose has been described. On the contrary, genome analysis predicted N-glycosylation to be a common post-translational modification in archaea (Kaminski *et al.*, 2013). Archaeal N-glycosylated proteins share several common features with bacteria and eukaryotes. Similarly to bacteria, archaea produce a wide diversity of N-glycan structures, for which an increasing number are now reported (Kärcher *et al.*, 1993; Voisin *et al.*, 2005). There is however no apparent structural uniformity between them, even if specific features seem to be associated with the different habitats of these organisms (Calo *et al.*, 2010).

Several archaeal structures contain methylated mannosyl residues. For instance, the S-layer glycoprotein from *Methanothermobacter feravidus* V24S DSM 2088 holds an α -D-3-O-methyl-Man β -(1 \rightarrow 6)- α -D-3-O-methyl-Man β -(1 \rightarrow 2)-[α -D-Man β -(1 \rightarrow 2)]₃-(1 \rightarrow 4)-D-Gal β Nac hexasaccharide β -linked to Asn (Kärcher *et al.*, 1993). Archaeal N-glycans also often contain N-acetylated carbohydrates such as GlcNAc, GalNAc, or ManNAc, sulfated sugars, uronic acids, furanose forms of galactose and/or 2-acetamido-2,4-dideoxy-5-O-methyl-hexosulo-(1 \rightarrow 5)-pyranose, the first reported example of aldulose in a N-glycan structure (Ng *et al.*, 2011). Some archaeal N-glycans are also structurally close to those of eukaryotes. For instance, the N-glycans of the S-layer glycoprotein

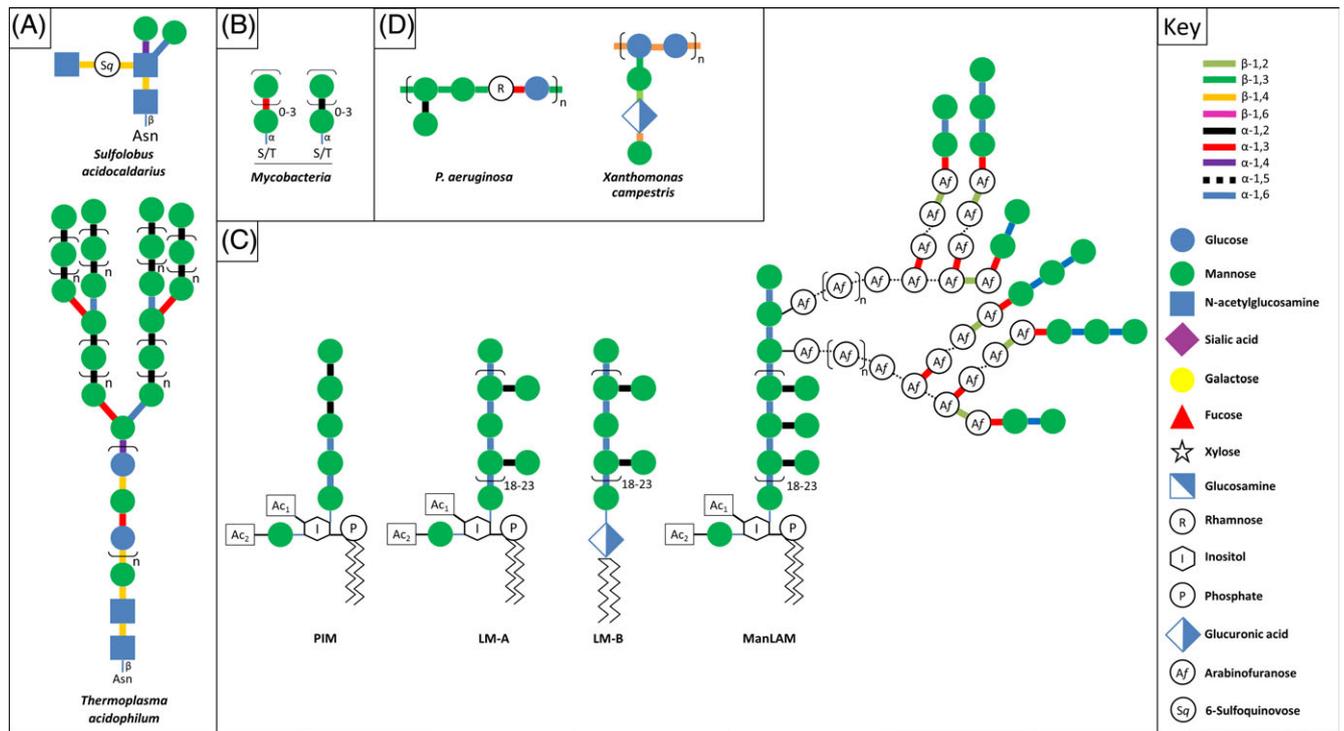


Fig. 3. Structure of mannosides from prokaryotes. (A) Archaeal N-glycans. (B) Bacterial O-glycans. (C) Lipoglycans found in actinomycetes. LAM, lipoarabinomannan; LM, lipomannan; PIM, phosphatidyl-myo-inositol mannoside. (D) Bacterial capsular polysaccharides.

from *Sulfolobus acidocaldarius* DSM639 are linked to Asn residues through a chitobiose moiety, the largest being 6-sulfoquinovose-Glc₁Man₂GlcNAc₂ (Peyfoon *et al.*, 2010) (Fig. 3A). Similarly, a *Thermoplasma acidophilum* ATCC25905 plasma membrane glycoprotein has been found to contain a highly mannosylated glycan with α-1,2, α-1,3 and α-1,6 linkages, linked to the Asn residues of proteins through a mannochitobiose trisaccharide (Yang & Haug, 1979) (Fig. 3A). These glycans play a key structural role, since the S-layer glycoprotein participates in cell shaping (Eichler & Adams, 2005). In addition, some archaeal species can survive without any active N-glycosylation pathway (Chaban *et al.*, 2006), while others can not (Meyer & Albers, 2013). However, the presence of a glycan coating is strongly associated with survival in harsh environments. For instance, variability in N-glycan pattern occurs in the halophilic archaeon *Haloferax volcanii* WR536 (H53), depending on the salt concentration (Guan *et al.*, 2012), while the extreme halophile *Halobacterium halobium* DS2 produces sulfated or uronic acids containing N-glycans in the presence of high salt concentrations (Mengele & Sumper, 1992). Finally, in archaea, N-glycans are attached to proteins in the same N-x-S/T (x≠P) sequon as in eukaryotes, although an additional N-x-N/L/V sequon has also been reported in *Halobacterium halobium* DSM670 (Zeitler *et al.*, 1998).

O-glycosylation occurs both in bacteria and archaea. For the latter, however, few studies exist and O-glycan structures have only been reported in *Halobacterium salinarum*

ATCC19700 and *Haloferax volcanii* WR536 (H53), where a Glc-α-1,2-Gal disaccharide is found attached to serine and threonine (Mescher & Strominger, 1976; Sumper *et al.*, 1990). In bacteria, by contrast, O-glycosylation has been reported many times, and an increasing amount of structural detail is available. Most of the known O-glycans containing mannosyl residues were identified from actinomycete glycoproteins, with a particular focus on the human pathogen *Mycobacterium tuberculosis*. Many are immunologically active molecules making an important contribution to virulence and to host–bacteria interactions (Nandakumar *et al.*, 2013). O-mannosylation in actinomycetes resembles that of yeasts. For example, the *Mycobacterium tuberculosis* ATCC35801 Apa protein has been found to be O-mannosylated on multiple S/T in Pro-rich C- and N-terminal domains with 1–3 α-1,2 linked mannosyl residues (Dobos *et al.*, 1996), and glycans containing up to 10 α-1,3-linked mannosyl residues have been identified in the MPB83 protein from *Mycobacterium bovis* BCG (Michell *et al.*, 2003). Several other bacteria were found to produce mannose-containing O-glycans, including *Corynebacterium glutamicum* ATCC13032 (Hartmann *et al.*, 2004), *Streptomyces coelicolor* J1929 (Wehmeier *et al.*, 2009), *Streptococcus gordonii* M99 (Takamatsu, Bensing & Sullam, 2004), and even a Gram-negative bacterium such as *Bacteroides fragilis* YCH46 (Fletcher *et al.*, 2009) (Fig. 3B).

GPI-anchored proteins have been identified in archaeal species but to date not in bacteria (Kobayashi, Nishizaki & Ikezawa, 1997; Eisenhaber, Bork & Eisenhaber, 2001).

Little is known about their structure, function and biosynthesis processes. However, it seems likely that they are closely related to the eukaryotic GPI anchor both in terms of their structure and function, since many archaea where GPI-anchored proteins have been identified are closely related to eukaryotes. However, *Methanosarcina barkeri* DSM800 produces glucosaminyl archaetidylinositol, a molecule closely related to GPI found in the eukaryote GPI anchor, suggesting that as for N-glycans, some small structural discrepancies are present between eukaryotes and prokaryotes (Nishihara *et al.*, 1992).

Mannoglycolipids are present in many prokaryotes, with the most striking example in the pathogen *Mycobacterium tuberculosis*. The mycobacterial cell envelope forms more than 60% of the cell dry mass. It contains an exceptionally high level of mannosylated compounds. Among these, phosphatidyl-myo-inositol mannosides (PIMs), lipomannan (LM) and lipoarabinomannan (LAM) are of particular interest because of their strong involvement in pathogenicity (Kaur *et al.*, 2009) (Fig. 3C). They are structurally related to the LPS found in certain *Leishmania* species (see Section II.1d). A detailed review of their structure and biosynthesis can be found in Kaur *et al.* (2009). These molecules share a common phosphatidyl-inositol lipid anchor with some variations regarding the number, location and nature of the fatty acids (Gilleron *et al.*, 2008). PIMs contain a mannosylated extension of 1–6 mannosyl residues, named PIM_{1–6}. The inositol molecule can hold α -Man β on position 2, while position 6 holds a chain of 5 α -1,6 and α -1,2 mannosyl residues. Two additional acyl chains can be added to position 3 of the inositol and to the C₆-OH of the mannosyl linked to position 2, to yield Ac₁PIM_n and Ac₂PIM_n, respectively (Fig. 3C). The LM molecule differs slightly from PIMs in that the mannosyl chain linked to position 6 of the inositol is much longer (20–25 residues) and only contains α -1,6 linkages (Kaur *et al.*, 2007). This chain can hold α -1,2 ramifications, but the branching positions are not yet elucidated. In addition, LAM contains an arabinan motif linked to some non-terminal mannosyl residues of the mannan core (Shi *et al.*, 2006). The arabinan polymer contains around 60–70 arabinofuranosyl residues depending on the species, consisting of a main chain of α -1,5 linkages with α -1,3-linked ramifications. This structure can be terminally α -1,5 mannosylated, or hold α -1,2 Man₂ or Man₃ capping the arabinofuranosyl chains to form the ManLAM molecule found in *M. tuberculosis* (Fig. 3C). These glycolipids are conserved among Corynebacteria, but another LM type has been identified both in *M. tuberculosis* H37Rv and *C. glutamicum* ATCC13032 (Lea-Smith *et al.*, 2008). It is closely related to the LM described above (hereafter LM-A) which is termed LM-B. The glycan part is similar to LM-A, but it is anchored through a glucuronic acid diacylglycerol (Fig. 3C). The significance of this mannolipid to this pathogen remains to be assessed.

Unlike its cell wall, the mycobacterial capsule contains 95–99% proteins and glycans (Ortalo-Magné *et al.*, 1995). Among the latter, three types are found: α -1,4-glucan, arabinomannan, and mannan. α -1,4-glucan represents 80%

of the total carbohydrate content and its molecular mass reaches 100000 Da. Arabinomannan is structurally similar to the lipid-anchored LAM, while mannan is composed of α -1,6 mannosyl residues (Ortalo-Magné *et al.*, 1995). This mannan chain has some branches consisting of α -1,2-linked mannosyl residues, making it structurally closely related to the mannan chain of lipid-anchored arabinomannan.

Many prokaryotes also secrete extracellular components, such as proteins, signalling molecules, and polysaccharides. The opportunistic pathogen *Pseudomonas aeruginosa* produces the Psl polysaccharide, which consists of a repeated pentasaccharide containing D-mannosyl, D-glucosyl and L-rhamnosyl residues (Byrd *et al.*, 2009), with a molecular mass of $0.5\text{--}2 \times 10^6$ Da (Fig. 3D). Another example is the biofilm formed by the plant pathogen *Xanthomonas campestris*. This bacterium produces a polymer called xanthan, which participates in plant invasion and virulence of the bacterium. It is well known for its applications in the food industry as a thickener or viscosifier. Xanthan is formed by a main chain of cellulose, β -1,3 branched every two glucosyl units by the trisaccharide β -D-Man β -(1 \rightarrow 4)-D-Glc β A-(1 \rightarrow 2)-D-Man β (Fig. 3D). The two mannosyl residues are derivatized by additional pyruvic and acetyl groups (Crossman & Dow, 2004).

III. RECOGNITION OF EUKARYOTIC MANNOSIDES BY BACTERIA

Almost every living organism synthesizes mannosylated glycoconjugates and/or polysaccharides, which are exposed to the outside environment. When any cell meets another cell, it thus necessarily contacts its surrounding glycan coat. Herein, we consider only the interactions occurring between bacteria and the mannosides they may encounter in their environment. Bacterial–mannoside interactions may either induce a ‘positive’ reaction, such as symbiosis or mutualism, which generally does not imply glycan degradation, or a ‘negative’ one, such as pathogenicity, parasitism or even commensalism, where bacteria feed on the glycans produced by other living cells, triggering defence mechanisms.

Depending on their ecosystem, bacteria are exposed to different mannoside structures. In all cases, carbohydrate recognition involves specific proteins which can be directly coupled to degradation mechanisms, or induce a cascade of signal transduction processes. In carbohydrate harvesting, mannoside recognition can be directly associated with degradation, i.e. when the receptor is physically connected to the breaking-down activity, as in the case of carbohydrate binding modules (CBMs), which enhance enzymatic efficiency by guiding the catalytic domain towards its substrate (Zhang *et al.*, 2014). CBMs that are specific to β -mannosides are classified into nine families of the carbohydrate active enzymes database (CAZy, www.cazy.org; Lombard *et al.*, 2014): CBM16, 23, 27, 35, 59 and CBM26 harboured by β -mannanases of the glycoside hydrolases (GHs) 5 and GH26 families, CBM13 found

in plant lectins that bind mannose, CBM29 found in a non-catalytic component from *Piromyces equi* strain IMI CC number 375061, and the CBM_NC appended to GH26 mannanase from *Cellvibrio japonicus* Ueda107.

During the last decade, several integrative studies based on genomic, transcriptomic, biochemical and structural analyses of glycan catabolic pathways revealed that in bacteria, mannoside recognition and degradation also involve membrane-anchored receptors, which activate a signal cascade ultimately initiating or enhancing the production of appropriate glycan catabolic enzymes. These receptors are multi-component systems. They are encoded together with mannoside-degrading enzymes by multigenic systems such as the polysaccharide utilization loci (PUL) characterized in Bacteroidetes and recently referenced in the PUL database (Terrapon & Henrissat, 2014), which is a highly useful resource to assess glycan catabolic functions in these organisms. Mannoside-specific PUL-like systems recently have been characterized, mainly in *Bacteroides* species but also in other bacteria (Martens, Chiang & Gordon, 2008; Sonnenburg *et al.*, 2010; Martens *et al.*, 2011; Senoura *et al.*, 2011; Kawahara *et al.*, 2012; McNulty *et al.*, 2013; Abbott *et al.*, 2015; Cuskin *et al.*, 2015b). These genomic loci code for polysaccharide utilization systems which resemble the starch utilization system (Sus) found in *Bacteroides thetaiotaomicron* VPI-5482 (Reeves, Wang & Salyers, 1997; Shipman, Berleman & Salyers, 2000; Cho *et al.*, 2001). Sus-like systems are multiple cell-envelope-associated protein complexes used for sensing, binding, and subsequent depolymerization of complex carbohydrates. Starch recognition is mainly performed by the membrane-associated SusC and SusD proteins, providing 60% of total starch binding affinity, the remainder provided by additional recognition mediated by SusE and SusF (Shipman *et al.*, 2000). The crystal structure of the complex SusE–SusF and starch was recently described, highlighting that they are formed by tandem repeats of starch-binding modules, providing a strong affinity towards starch, and allowing accommodation of the three-dimensional (3D) starch structure (Cameron *et al.*, 2012). A similar mechanism targeting yeast mannosides by *Bacteroides thetaiotaomicron* VPI-5482 has been recently characterized. In the latter, two proteins (a SusD-like protein and a surface glycan binding protein specific for mannose) are involved in mannoside recognition and sequestration (Cuskin *et al.*, 2015b). The 3D structure of the binding element of a probable β -mannan degradation pathway in the thermophilic anaerobic bacterium *Caldanaerobius polysaccharolyticus* ATCC BAA-17 also has been described (Chekan *et al.*, 2014). Here, mannobiose and mannotriose recognition involves a solute-binding component of an ATP-binding cassette (ABC) transporter.

For the mannoside-utilization systems described above, recognition of plant and yeast mannans by bacteria has a clear goal: their assimilation. However, interactions between bacteria and eukaryotic mannosides are also implicated in cell adhesion, in most cases prior to invasion. For that purpose, many bacteria harbour carbohydrate-binding proteins

belonging to the class of lectins often found in fimbriae (or pili). Contrary to CBMs, these mannoside-binding proteins are not classified in the CAZy database, because they are not part of CAZyme amino acid sequences. Fimbriae are formed by polymerization of pilin proteins. They are widespread in Gram-negative bacteria and are responsible for adhesion to host cells, mostly through binding of glycoproteins (Lebeer, Vanderleyden & De Keersmaecker, 2010). Different classes of fimbriae have been reported, but the archetypal is type 1 fimbriae. Its structure forms an extracellular appendage whose top protein, FimH, has been demonstrated to bind mannosyl residues strongly (Bouckaert *et al.*, 2005; Wellens *et al.*, 2008; Korea, Ghigo & Beloin, 2011). Type 1 fimbriae have been implicated in the specific adhesion of various enterobacteria to human epithelial cells (Grzymajko *et al.*, 2013). They were also found associated with membranous cells, a class of cells found in Peyer's patches in the gut epithelium, which are linked with antigen transportation through the specific involvement of glycoprotein 2, a highly N-glycosylated protein (Ohno & Hase, 2010). In addition, type 1 fimbriae are critical for the proper attachment of bacterial cells to mannose-containing extracellular polysaccharides found in biofilms (Rodrigues & Elimelech, 2009).

IV. MANNOSIDE DEGRADATION BY BACTERIA

Degradation of mannosides is widespread in the microbial world. Mannoside hydrolysis involves various enzymes, of which mannanases and mannosidases are the best known. Mannosidases are enzymes involved in the degradation of non-reducing terminal mannosyl residues, while mannanases are endo-acting enzymes, involved in the degradation of mannosides with a high degree of polymerization. These enzymes are widely distributed in micro-organisms, being produced by both bacteria and fungi. A list of characterized mannoside-degrading enzymes is provided in Table S1. Many more bacterial mannoside-degrading enzymes have been identified and characterized than fungal ones, for which the functional diversity is restricted to the degradation of plant cell wall mannans. The properties of these fungal enzymes are reviewed elsewhere (Furquim Da Cruz, 2013; Kubicek, Starr & Glass, 2014; Rytioja *et al.*, 2014), therefore the present review will focus on mannoside degradation by bacteria. As listed in Table S1, β -mannanases and β -mannosidases involved in plant β -mannan catabolism or in degradation of particular motifs of yeast or mammal N-glycans, are found in many GH families of the CAZy classification: GH1, GH2, GH5, GH26, GH113, and GH130. α -mannosidases and α -mannanases, acting specifically on mammal and yeast N-glycans, are classified in the GH families GH76, GH31, GH38, GH47, GH63, GH92, GH99 and GH125. In addition, new mannoside degradation pathways have been reported recently, involving β -mannoside phosphorylases classified in the GH130 family. This is the sole known enzyme family implicated in

mannoside breakdown by phosphorolysis. Contrary to glycoside hydrolases, for glycoside phosphorylases (GPs) cleavage of the glycan interosidic bonds occurs with concomitant phosphorylation of the glycosyl residue released from the glycan non-reducing end. The number of sequences clustered in the GH130 family has been rapidly expanding over recent years, and today contains 865 members, separated into 3 subfamilies (Ladevèze *et al.*, 2013; Cuskin *et al.*, 2015a). Like all mannoside-degrading GHs, GPs of the GH130 family act synergistically with GHs of various specificities. Indeed, as described in Section II, mannosides are rarely composed exclusively of mannosyl residues. On the contrary, they are often associated with other glycosyl residues, and types of osidic linkages. Therefore, in order to achieve mannoside degradation, bacteria produce a highly diverse panel of glycan-degrading activities, of which the specificities are directly related to the mannoside structures they have to face in their specific environment.

(1) Mammal gut bacteria

Glycan degradation by gut bacteria has been studied extensively. In particular, the human gut microbiota has received recent attention, as it is directly involved in human health. Gut bacteria belonging to the genus *Bacteroides* are prominent glycan degraders, due to the extreme diversity of CAZymes they produce, allowing them to feed on various dietary and host polysaccharides (Martens *et al.*, 2009).

Mammal gut bacteria directly can access plant mannosides, which are part of 'dietary fibre'. In the human gut, dietary mannans are mainly found in the cell walls of grains and nuts. Several examples of plant β -mannan degradation pathways have been reported, involving mannoside hydrolases and mannoside phosphorylases. For instance, *Bacteroides fragilis* NCTC 9343, a prominent human gut bacterium, possesses a PUL dedicated to mannan assimilation. Constituting an operon, *BF0771–BF0774* genes encode the putative GH26 mannanase ManA, the GH130 mannosylglucose phosphorylase *BfMGP* (Senoura *et al.*, 2011), a putative sugar/cation symporter, and a cellobiose 2-epimerase (Ojima *et al.*, 2011). As for *RmMGP*, *BfMGP* phosphorylates β -D-Manp-1,4-D-Glc into Man1P and glucose in the presence of inorganic phosphate. The research of Senoura *et al.* (2011), which led to the creation of the GH130 family in the CAZy database, unravelled a unique mannan assimilation pathway. The authors proposed a similar model to that described for *RmMGP*, in which the GH26 mannanase produces mannoside units from mannan degradation, which are translocated by the BF0073 symporter to undergo subsequent epimerization into Man-Glc, followed by its phosphorolysis into Man1P and glucose. The end products reach the central metabolism either directly (for glucose), or after being converted into mannose-6-phosphate and fructose-6-phosphate by phosphomannose mutase and phosphomannose isomerase (Fig. 4A1).

A similar pathway has been identified in other mammal gut bacteria, like *Ruminococcus albus* 7, a ruminal anaerobic bacterium which efficiently degrades plant β -mannan using two synergistic GH130 mannoside phosphorylases (Kawahara *et al.*, 2012). These two enzymes, *RaMP1* and *RaMP2*, act on β -D-Manp-(1 \rightarrow 4)-D-Glc and β -1,4-manno-oligosaccharides, respectively. *RaMP1*, a *BfMGP* ortholog, is thought to participate in the same mannan degradation pathway together with a GH26 β -mannanase and a cellobiose 2-epimerase (Fig. 4A1). *RaMP2* is different. In addition to being able to process β -1,4-linked manno-oligosaccharides, it showed a much wider tolerance to acceptor sugars in reverse-phosphorolysis reactions. Although it is able to phosphorolyse Man-Glc, its natural substrates were demonstrated to be the imported β -1,4-linked manno-oligosaccharides generated by the GH26 mannanase. These manno-oligosaccharides would therefore be processed by *RaMP2* to yield α -D-mannose-1-phosphate (Man1P) and β -1,4-linked manno-oligosaccharides of reduced chain length, ultimately β -1,4-mannobiose, converted into Man-Glc and then processed by *RaMP1*.

Relying on their host to ensure their survival, gut bacteria developed other strategies to survive in the event of host starvation. When dietary components are lacking, gut bacteria such as *Bacteroides thetaiotaomicron* VPI-5482 can grow on eukaryotic glycans, especially those found in the heavily glycosylated mucin proteins continuously secreted by the host's epithelium (Martens *et al.*, 2008).

N-glycan foraging starts in the mammalian oral cavity. The pathogen *Capnocytophaga canimorsus* 5 possesses a large transmembrane multi-protein complex involved in deglycosylation of complex N-glycans in human immunoglobulin G (IgG) (Renzi *et al.*, 2011). This organism contains a multigenic cluster coding for five proteins forming the glycoprotein deglycosylation complex (GpdC–G), and sharing homology with Sus binding proteins. All are membrane-anchored proteins associated in a stable complex. This complex has been demonstrated to deglycosylate human IgG *in vitro*, the catalytic protein being GpdG, a *N*-acetylglucosaminidase. One of the multiproteic constituents, GpdC, is a porin-like protein, probably involved in import of the released N-glycan to the periplasmic space. In addition, SiaC, a periplasm-orientated membrane-anchored sialidase, probably removes the capping sialic acids of the complex and hybrid N-glycans. Unidentified periplasmic glycoside hydrolases could then hydrolyze the internalized N-glycan.

Many other gut bacteria are also able to feed on host N-glycans. Several recent studies targeted N-glycan metabolism by human intestinal bacteria, which might be linked with inflammatory bowel diseases. These studies revealed that N-glycan metabolism involves both glycoside hydrolases and phosphorylases (Renzi *et al.*, 2011; Ladevèze *et al.*, 2013; Nihira *et al.*, 2013).

Several *Bacteroides* species harbour GH130 enzymes involved in human N-glycan metabolism. The human gut symbiont *B. thetaiotaomicron* VPI-5482 possesses a GH130

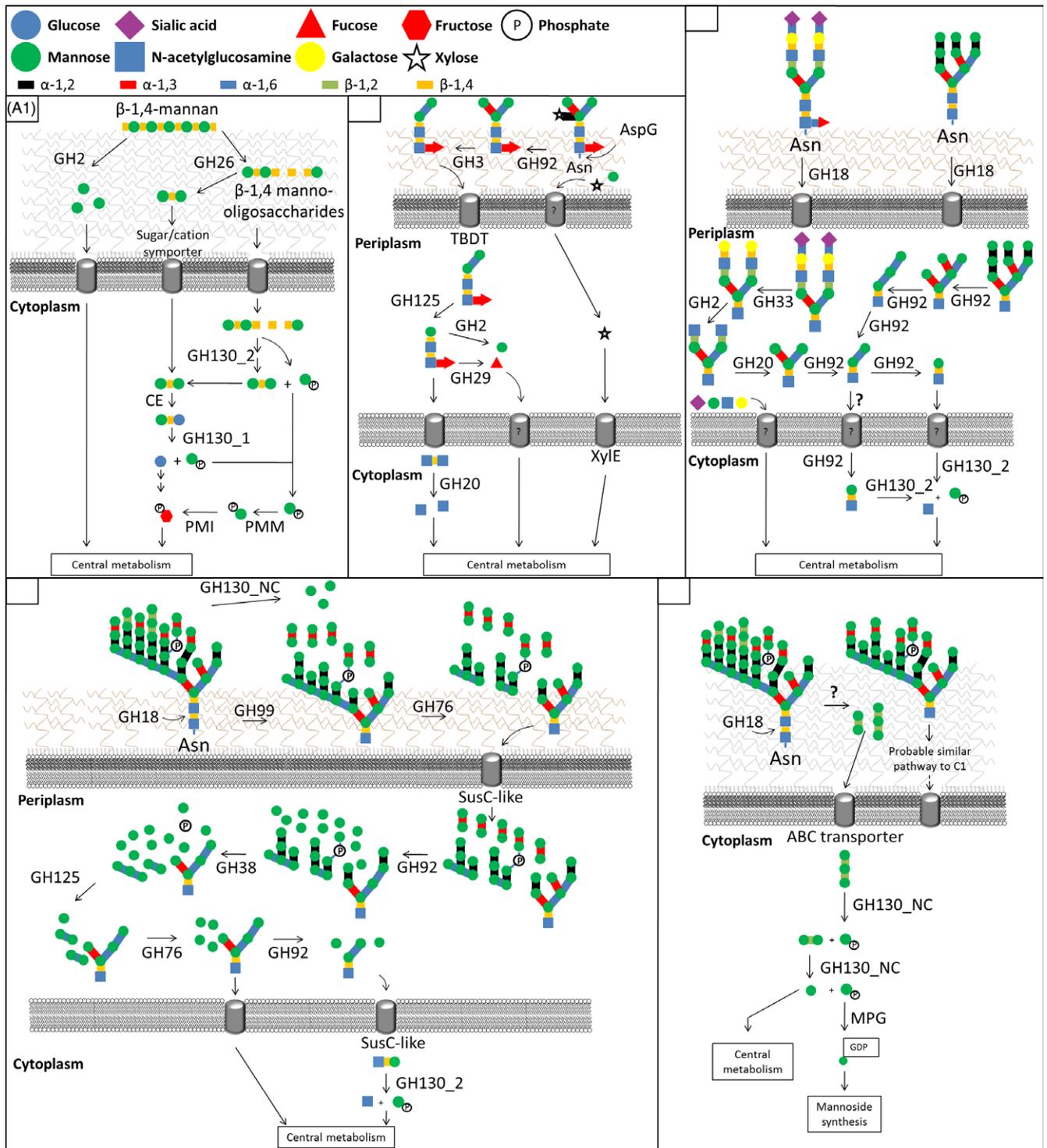


Fig. 4. Pathways for mannoside degradation. (A1) Plant β-1,4-mannan degradation by a Gram-positive bacterium such as *Ruminococcus albus* 7 (Kawahara *et al.*, 2012); (A2) plant N-glycan degradation by a Gram-negative bacterium such as *Xanthomonas campestris* *pv.* *campestris* (Dupouiron *et al.*, 2015). (B) Human high mannose (HMNG) and complex N-glycan (CNG) degradation by Gram-negative bacteria such as *Bacteroides fragilis* NCTC 9343 (Ladevèze *et al.*, 2013; Nihira *et al.*, 2013). (C1) Fungal N-glycan degradation by a Gram-negative bacterium such as *Bacteroides thetaiotaomicron* VPI-5482 (Cuskin *et al.*, 2015b). (C2) *Candida albicans* β-1,2-mannoside-containing N-glycan degradation coupled with GDP-Man synthesis, for a Gram-positive bacterium such as *Thermoanaerobacter* sp. X514 (Chiku *et al.*, 2014; Cuskin *et al.*, 2015a). ABC transporter, ATP-binding cassette transporter; CE, cellobiose 2-epimerase; MPG, mannosylphosphate glucuronyltransferase; PMI: phosphomannose isomerase; PMM, phosphomannose mutase; SusC, starch utilization system C protein; TBDT, TonB-dependent transporter; XylE, D-xylose-proton symporter.

mannoside phosphorylase specific to the disaccharide β -D-Man β -1,4-D-Glc β NAc, a N-glycan core motif (gene ID: AAO76140). The analysis of the surrounding genes present in its PUL revealed the presence of four GH92, GH20, GH33 and GH18 glycoside hydrolases assigned to α -mannosidase, β -N-acetylhexosaminidase, exo- α -sialidase, and endo- β -N-acetylglucosaminidase activities, which would act synergistically to break down host N-glycans completely (Nihira *et al.*, 2013). In addition, this gene cluster encodes a major facilitator superfamily transporter, a protein of unknown function, an outer membrane lipoprotein and a TonB-dependent oligosaccharide transporter. Based on these elements, Nihira *et al.* (2013) developed a model of N-glycan metabolism (Fig. 4B). The presence of a putative sialidase, together with endo- β -N-acetylglucosaminidase activities, led the authors to propose a specific degradation of CNGs. The proposed model is in accordance with the characteristics of Sus-like systems encountered in *Bacteroides* species (Terrapon & Henrissat, 2014). First, the N-glycan would be bound by the SusC/D homologues and released from the protein by the action of GH18 endo- β -N-acetylglucosaminidase. Contrary to plant N-glycan degradation described in Section IV.3, deglycosylation of the host protein would retain one N-acetylglucosamine residue bound to the protein. Sequestration of the N-glycan into the periplasm would allow for subsequent deconstruction by the action of either characterized GH92 α -mannosidase or the hypothesized α -sialidase, β -galactosidase and β -N-acetylhexosaminidase (Zhu *et al.*, 2010). The resulting β -D-Man β -1,4-GlcNAc disaccharide would finally be internalized by a predicted transporter before being processed by the Bt1033 GH130 (Fig. 4B).

Finally, the human gut bacterium *B. thetaiotaomicron* VPI-5482 was reported to feed on yeast mannan, a component of the human diet (Cuskin *et al.*, 2015a,b) via its highly complex enzymatic machinery encoded by three PULs (PUL_36, PUL_68 and PUL_69 in the PUL database classification; Terrapon *et al.*, 2014). Biochemical characterization of the 15 proteins encoded by these PULs allowed deduction of the precise mechanism by which this bacterium is so efficient in metabolizing yeast mannans in the human gut. These PULs, orchestrated around SusC/D homologues to bind and sequester mannosides, mainly code for GH92, GH76, GH99 or GH125 α -mannosidases. The degradation model is similar to that for Bt1033-containing PUL for complex N-glycan foraging (Fig. 4C1). However, in the latter, many extracellular α -mannosidases are involved in the limited, but sufficient, degradation of α -1,2 side chains, thus suppressing the sterical restraint that would prevent GH18 endo- β -N-acetylglucosaminidase from releasing the glycans from the protein, and their subsequent translocation to the periplasm. Additional periplasmic α -1,2, α -1,3 and α -1,6 mannosidases have been demonstrated to act in a sequential manner progressively to release mannosyl units that are imported to the cytosol.

The *B. thetaiotaomicron* PULs also encode for GH130 enzymes that are involved in yeast mannan degradation.

This CAZyme family is thus highly specific to eukaryotic β -mannoside degradation, all its characterized members targeting either plant β -1,4-mannans, the core β -D-Man β -(1 \rightarrow 4)-GlcNAc disaccharide of human N-glycans or yeast β -1,2-mannans. Analysis of GH130 containing PUL-like structures at the scale of the human gut microbiome allowed the definition of the GH130 family in three protein sequence clusters (Ladevèze *et al.*, 2013). The GH130_1 subfamily, which contains *Ra*MP1, *Rm*MGP, and *Bf*MGP, is specifically encoded in PULs also containing genes coding for GH5 mannanases and GH26 mannosidases, and was therefore associated with plant β -mannan degradation. The GH130_2 subfamily, which contains Bt1033 and Uhg β _MP (another mannoside phosphorylase belonging to an unknown human gut bacterium assigned to the *Bacteroides* genus), are encoded by PULs encoding other enzymes possessing activities required for degradation of mature and immature CNGs and HMNGs, namely the GH92 α -mannosidases and GH18 N-acetylglucosaminidases. Specifically, Uhg β _MP, identified by high-throughput functional screening of the human gut metagenome (Tasse *et al.*, 2010), showed high affinity for β -D-man β -1,4-D-Glc β NAc, the core disaccharide of all N-glycans (Ladevèze *et al.*, 2013) (Fig. 4B). Analysis of the tertiary and quaternary structures of Uhg β _MP recently allowed identification of specific features that are responsible for its promiscuity (Ladevèze *et al.*, 2015). This enzyme is indeed efficient in the degradation and synthesis by reverse-phosphorolysis of various β -1,4 manno-oligosaccharides, and is the sole known mannoside phosphorylase active *in vitro* on plant β -1,4-mannan. The substrate flexibility of GH130_2 enzymes towards β -mannosides may indicate that these enzymes, and some of their partners encoded by the same PULs, could break down a large range of β -mannosides during substrate starvation or substrate overabundance. These enzymes could thus be associated with the metabolic flexibility of bacteria. This would explain why expression of a GH130_2 enzyme (BACOVA_04110) from the prominent gut bacterium *Bacteroides ovatus* ATCC 8483 is induced when the strain is grown on plant β -1,4-mannan, while its gene belongs to PUL85, which also harbours GH18- and GH92-encoding genes related to N-glycan breakdown (J. Despres, P. Mosoni, S. Ladevèze, E. Laville & G. Potocki-Veronese, unpublished data). PUL85 was also up-regulated in plant-fed mice (Martens *et al.*, 2011). Substrate flexibility may not be restricted to GH130_2 enzymes, but may also be a trait of other GH130 sequences, which do not show sufficient homology to be grouped under a unique subfamily but are grouped instead in a non-classified group of sequences (GH130_NC). Based on the genomic context of the GH130-encoding genes, on the presence or absence of a signal peptide, and on the results of recent biochemical and structural studies, it is nevertheless possible to predict the catalytic mechanism and substrate specificity of these GH130_NC enzymes. Extracellular GH130 members lacking the conserved basic residues involved in phosphate binding by mannoside phosphorylases would be β -mannoside hydrolases. This is the case for the GH130_NC enzymes

Bt3780 and *BACOVA_03624* from *B. thetaiotaomicron* and *B. ovatus*, and also for the recently characterized *Dfer_3176* enzyme from the plant-associated bacterium *Dyadobacter fermentans* (Nihira *et al.*, 2015). As *Bt3780* and *BACOVA_03624* genes encode enzymes targeting $\text{Man}\beta\text{-}\beta\text{-(1}\rightarrow\text{2)-Man}\beta$ linkages (Cuskin *et al.*, 2015a), their physiological role would be the break down of cell wall mannans of gut fungi. The physiological function of their homolog in *Dyadobacter fermentans* is still not elucidated, although it was shown to target the same $\text{Man}\beta\text{-}\beta\text{(1}\rightarrow\text{2)-Man}\beta$ substrate *in vitro*.

These mechanisms of mannose harvesting by gut bacteria appear to be very common, and not restricted to well-studied cultured species. Thanks to the huge metagenomic initiatives dedicated to the characterization of mammal gut microbiomes, it is now possible to assess the abundance of such catabolic pathways in these complex ecosystems. It was thus shown that mannoside-associated PULs closely related to those from *B. thetaiotaomicron* and other *Bacteroides* species are highly abundant and prevalent in the human gut microbiome (Ladevèze *et al.*, 2013; Cuskin *et al.*, 2015b). The inventory of the loci and genes coding for mannoside-degrading enzymes in other cultivated and metagenomic species will certainly provide new insights on mannoside-degrading mechanisms in the vast world of bacteria.

(2) Soil and spring bacteria

Plant and algal β -mannans are among the preferred substrates of bacteria living in soil and water (Moreira & Filho, 2008). β -mannan degradation is generally carried out by a cocktail of β -mannanases and β -mannosidases (Stoll, Ståhlbrand & Warren, 1999), of which some have been crystallized (Le Nours *et al.*, 2005). Additional GH1, GH3, GH5, GH9, GH30, or GH116 β -glucosidases, GH4, GH27, GH36, GH57, GH97 or GH110 α -galactosidases (Luonteri, Tenkanen & Viikari, 1998) are often involved to ensure complete assimilation of gluco- and galactomannans (Duffaud *et al.*, 1997). These enzymes are often permanently expressed at a basal level, and associated with CBMs in order to sequester polymeric substrates that cannot be internalized by the cells because of their high degree of polymerization (Zhang *et al.*, 2014).

Recently, two PUL-like systems involved in β -mannan degradation by *Caldanaerobius polysaccharolyticus* ATCC BAA-17, a thermophilic bacterium isolated from hot-spring sediments, have been discovered using transcriptomics (Chekan *et al.*, 2014). These two multigenic systems together allow complete mannan metabolization. The organization of these loci resembles that of *Bacteroidetes* PULs related to mannan assimilation and regulation. Each of them contains a GH5 β -mannanase, *Man5A* and *Man5B*. *Man5A*, a membrane-anchored protein expressed at basal levels, produces large manno-oligosaccharides, which are sensed by transcriptional regulators encoded by both mannan-associated loci (Cann *et al.*, 1999). They also encode permeases that are probably involved in the import of these manno-oligosaccharides. The *Man5B* protein lacks a signal

peptide, which also suggests that subsequent steps of mannan metabolization occur intracellularly. Interestingly, each locus contains a putative β -manno-oligosaccharide phosphorylase belonging to the recently created GH130 family (Senoura *et al.*, 2011).

Another mannoside-degrading soil bacterium was recently discovered in *Thermoanaerobacter* sp.X-514. It was shown specifically to target yeast β -1,2-linked manno-oligosaccharides and to harbour two GH130-encoding genes (Chiku *et al.*, 2014). The genomic environment of these two genes led Chiku *et al.* (2014) to suggest that the two β -1,2-oligomannan phosphorylases are part of a salvage pathway for GDP-mannose biosynthesis, as they are surrounded by a GH5 β -glycoside hydrolase and a mannosyltransferase belonging to family 4 of the glycosyltransferases (GTs) (Fig. 4C2). In the proposed model, an ABC transporter found in the same gene cluster would import β -1,2 manno-oligosaccharides extracted from phosphopeptidomannan found in the yeast *C. albicans*, or from intracellular β -1-2 manno-oligosaccharides of *Leishmania mexicana* (Ralton *et al.*, 2003). The specificity of these GH130 β -1,2 mannosyltransferases and β -1,2 manno-oligosaccharide phosphorylases, named *Teth514_1789* and *Teth514_1788*, respectively, would allow for production of α -D-mannose-1-phosphate from the imported β -1,2 manno-oligosaccharides, thus feeding the GT4 GDP-mannosyltransferase. This study constitutes the sole reported example of a mannoside degradation mechanism coupled to a biosynthetic pathway (Chiku *et al.*, 2014).

The GH130 mannosyl-glucose phosphorylase *RmMGP*, isolated from the alkaline hot spring *Rodothermus marinus* ATCC 43812 bacterium (Jaito *et al.*, 2014), degrades the β -1,4 bond of the β -D-*Man* β -1,4-D-*Glc* (*Man-Glc*) motif of plant glucomannans. Based on the analysis of the genomic locus encoding *RmMGP*, *RmMGP* would be involved in β -mannan degradation, similarly to what was proposed for its *Bacteroides fragilis* and *Ruminococcus albus* (human gut and ruminal bacteria) orthologs. Indeed, the genomic environment is conserved among these bacteria, and contains a cellobiose 2-epimerase and two GH26 mannanases. In this model (Fig. 4A1), β -1,4-mannobiose units are generated from mannans by GH26 mannanases, which are imported through a conserved transporter and subsequently converted into *Man-Glc* by the cellobiose 2-epimerase. The *Man-Glc* disaccharide is degraded by *RmMGP* into *Man1P* and glucose, which feeds the central metabolism. The generated *Man1P* molecules are then converted into mannose-6-phosphate by phosphomannomutase, then into fructose-6-phosphate by phosphomannose isomerase (Jaito *et al.*, 2014).

(3) Plant-associated bacteria

In addition to hemicellulose β -mannans, plant-associated bacteria also have access to plant N-glycans. Synergistic processes are required to degrade these complex structures efficiently. Recently, a full characterization of the bacterial plant pathogen *Xanthomonas campestris* *pv.* *campestris* ATCC

33913 N-glycan degradation PUL-like operon became available, demonstrating *in vitro* the sequential involvement of glycoside hydrolases in N-glycan degradation (Dupouiron *et al.*, 2015).

This PUL-like structure is composed of eight clustered genes, encoding the NixE–NixL proteins involved in the synergetic degradation of the plant-type α -1,3 fucosylated, β -1,2-xylosylated Man₃XylGlcNAc₂Fuc N-glycan. In this study, the eight targeted genes were cloned separately and expressed in order to elucidate their precise role in the deconstruction of this complex glycan. Enzyme characterization allowed the assignment of α -fucosidase, β -N-acetylglucosaminidase, β -mannosidase, β -xylosidase, α -mannosidase and β -galactosidase activities to each of the Nix proteins. All Nix enzymes contain a signal peptide but the use of type-II secretion system mutants revealed that NixG is intracellular, while NixK and NixI are the sole excreted glycoside hydrolases of this system, the other proteins being periplasmic. Based on this detailed analysis, the authors proposed a functional model for plant N-glycan degradation (Fig. 4A2). In this model, the extracellular GH92 NixK removes the α -1,3 mannosyl residue, followed by removal of the β -1,2 xylosyl residue by the GH3 NixI. Then, contrary to the situation in human pathogens, a hypothetical asparaginase (AspG) would release the glycan from the protein. TonB-dependent transporters would import the Man₂GlcNAc₂Fuc into the periplasm for further deconstruction. The GH125 NixJ would remove the α -1,6 mannosyl residue, followed by action of the GH2 β -1,4 mannanase. The resulting monomers and chitobiose molecules would be translocated to the cytosol through specific transporters, where NixG would hydrolyze the chitobiose molecule. Ultimately, the released GlcNAc molecules would enhance the expression of the Nix operon (Dupouiron *et al.*, 2015).

Finally, two GH130s from *Dyadobacter fermentans* DSM 18053 and *Listeria innocua* clip 11242 have been reported recently to exhibit β -1,2 mannosidase (Nihira *et al.*, 2015) and β -1,2 mannoside phosphorylase (Tsuda *et al.*, 2015) activities, respectively, but no biological function has yet been associated with these proteins.

V. DISCUSSION

The widespread distribution of mannosides in nature is indicative of their importance in biological processes. Being present in all kingdoms, these glycans are central elements of life, playing a key role as structural molecules, energy sources, and in cell–cell interactions.

To combat their structural diversity, bacteria have developed many complex catabolic pathways, involving various carbohydrate active enzymes efficiently to catalyse glycan assimilation and ensure metabolic regulation. These strategies, especially those of *Bacteroides* species, rely on dedicated PULs for complex glycan assimilation. These genomic loci, which have been the subject of great interest

in recent years, are often exchanged between bacteria by horizontal gene transfer (Lozupone *et al.*, 2008; Tasse *et al.*, 2010), which may underlie their ubiquitous distribution in ecosystems.

While the role of glycoside hydrolases in mannoside catabolism has been known for many years, a recently increasing number of studies have revealed the involvement of mannoside phosphorylases in plant, mammal, and yeast mannoside breakdown. Many anaerobic bacteria rely on their specific use to optimize energy consumption during glycan metabolization. Using phosphorolysis rather than hydrolysis may serve other purposes. Indeed, *Bacteroides fragilis* and other *Bacteroides* species lack the phosphotransferase sugar import system (Brigham & Malamy, 2005), an active transport system relying on the phosphorylation of imported simple sugars which generates a continuous flow of metabolites towards the cell, preventing carbohydrate leakage. Therefore, phosphorylation may serve both to save energy and maximize the rate of carbohydrate entry. Moreover, sugar-1-phosphate molecules are pivotal metabolites linking catabolic processes to anabolism, as most are substrates of nucleotidyl-transferases that yield nucleotide-activated sugars. These can be used by bacteria to produce a broad array of glycans through the action of classical Leloir glycosyltransferases which use nucleotide-activated sugars as glycosyl donors. The role of glycoside phosphorylases in glycan foraging is probably underestimated, due to the difficulty of differentiating them from real glycoside hydrolases and Leloir glycosyltransferases using only sequence-based functional genomics or metagenomics.

More generally, bacterial metabolization of mannosides is raising increasing interest, and reveals novel microbial pathways of mannose foraging. Particular efforts should be dedicated to the study of human glycan catabolism of pathogenic bacteria with the ultimate goal of controlling deleterious bacterial–host interactions. But in many habitats, microbial–host crosstalk is affected by the permanent fight for survival and, thus, by the ability of bacteria to feed on microbial and, in gut ecosystems, on dietary glycans. Even if the enzymatic machinery is now relatively well known for the catabolism of plant cell wall mannans and N-glycans, human HMNGs and CNGs, and a few fungal mannosides (the N-glycans of *S. cerevisiae* and *C. albicans* in particular), much remains to be discovered regarding the degradation of prokaryotic mannosides and eukaryotic O-mannans, lipophosphoglycans and GPI anchors. In addition, the structural diversity of mannosides is probably still underestimated. For instance, the human gut microbiota contains many different fungi (Hoffmann *et al.*, 2013), of which the N-glycan structures have not all been determined. One of the main challenges remaining is to accelerate the discovery of a large panel of mannoside-degrading enzymes, which are able to deconstruct these complex glycans. First, technological issues have to be overcome regarding activity-based screening strategies. The development of (i) chromogenic complex mannosides mimicking natural ones, and (ii) microfluidics, which requires very low amounts

of substrate, should allow a dramatic increase in the rate of enzyme discovery using functional genomics and metagenomics. This will also facilitate combinatorial enzyme engineering, which also requires high-throughput screens to explore sufficiently large sequence diversity. Because, as described herein, native bacterial enzymes act in cascades to deconstruct complex glycans in a stepwise manner, it is unlikely that any natural biocatalyst will be found that could release the complete glycoside constituents from glycoproteins. Engineering endo-acting CAZymes or even proteases to produce the most complex glycan structures possible (even linked to peptides) from cellular prokaryotic and eukaryotic extracts may thus open the way to a better understanding of how mannosides mediate cell–cell interactions.

VI. CONCLUSIONS

(1) Mannosides are ubiquitous molecules participating in numerous biological processes. They can act as structuring elements such as plant mannans or participate in protein shaping and function as well as in signalling when integrated in glycoconjugates. Mannoside structures are extremely diverse, especially for N-glycans and mannolipids, although some taxon-dependent structures of mannose-containing glycans are known. Much work remains to be done in order to identify and describe rare and novel mannosides, especially those of archae and extremophiles.

(2) The processes by which mannosides are degraded require specific recognition of mannoside structures. This involves specific carbohydrate-binding proteins acting as sensors to activate subsequent transport and degradation mechanisms, as well as specific domains associated with catabolic enzymes in order to guide them towards their substrate. Nevertheless, the relationships between the structural diversity and functions of these carbohydrate-binding proteins and modules remain understudied, and require extensive biochemical, genomic and transcriptomic analysis.

(3) Bacteria from various ecosystems have developed complex mechanisms to degrade the array of mannoside structures present in their environments. The mannoside catabolic machinery is encoded by gene clusters, also called polysaccharide utilization loci, of which expression is regulated by specific sensor proteins. Most of these gene clusters are the result of convergent evolution, or were subjected to horizontal gene transfers between bacteria. This regulation mechanism allows a series of endo- and exo-acting GHs and GPs, either intra- or extracellular, to act synergistically in order to deconstruct the mannoside structure in a stepwise manner, ensuring their assimilation through specific transporters. The role of many of these proteins in mannoside degradation by several Bacteroidetes species and some other bacteria has been recently revealed. But much remains to be discovered regarding the diversity of mannoside-specific CAZymes and transporters from other genera, especially those containing pathogens. Functional

genomics and microbiomics represent an opportunity to advance the discovery of these proteins and to expand our vision of the role of mannosides in cellular interactions, in particular between bacteria and their hosts.

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VIII. SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article.

Table S1. Current knowledge on mannoside-degrading enzymes.

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