

Review

Mucosal glycan degradation of the host by the gut microbiota

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Abstract

The gut microbiota plays a major role in human health and an alteration in gut microbiota structure and function has been implicated in several diseases. In the colon, mucus covering the epithelium is critical to maintain a homeostatic relationship with the gut microbiota by harboring a microbial community at safe distance from the epithelium surface. The mucin glycans composing the mucus layer provide binding sites and a sustainable source of nutrients to the bacteria inhabiting the mucus niche. Access to these glycan chains requires a complement of glycoside hydrolases (GHs) produced by bacteria across the phyla constituting the human gut microbiota. Due to the increased recognition of the role of mucus-associated microbes in human health, how commensal bacteria breakdown and utilize host mucin glycans has become of increased interest and is reviewed here. This short review provides an overview of the strategies evolved by gut commensal bacteria to access this rich source of the nutrient with a focus on the GHs involved in mucin degradation.

Key words: glycosylation, gut microbiota, mucin, mucus

Introduction

The gastrointestinal (GI) tract is home to a diverse range of microbial species collectively referred to as the gut microbiota which have a profound impact on host health. It is well established that the gut microbiota aids digestion of complex dietary polysaccharides which reach the colon undigested, enabled by the vast array of glycolytic enzymes encoded by gut symbionts (Zimmermann *et al.* 2019, El Kaoutari *et al.* 2013). In addition to dietary polysaccharides, gut microbes can utilize host glycans as a nutrient source. The ability to metabolize glycans such as human milk oligosaccharides, glycosaminoglycans and glycan moieties of glycoproteins and glycolipids found at mucosal surfaces grants bacteria a competitive advantage. This is particularly relevant to the microbial community that resides within the mucus layer of the large intestine.

The mucus layer is viewed as a defence mechanism, protecting the epithelial layer from microbes and other luminal compounds, but in the colon, mucus also plays a major biological function by harboring a distinct microbial community called the mucus-associated

microbiota. This is enabled by the bilayer organization of the colonic mucus which is divided into a stratified inner layer virtually impenetrable to bacteria and a loose outer layer providing a niche to microbes adapted to this environment (Johansson *et al.* 2008). This microbial community is tolerated due to the mutually beneficial relationship established with the host as a result of long-term coevolution (Neish 2009). Benefit to the host includes effective mucin turnover and stimulation of mucus production through Toll-like receptor-mediated interactions with sentinel goblet cells (Birchenough *et al.* 2016). Continuous mucus production is essential to maintain gut barrier function and is strengthened by the production of antimicrobial compounds against pathogenic bacteria (McGuckin *et al.* 2011). Other benefits of the mucus-associated microbiota include colonization resistance whereby pathogenic niches are already occupied by commensal species (Sorbara and Pamer 2019), and the production of metabolites directly implicated in the communication of microbes with the host. The mucus-associated gut microbiota can also significantly affect the development of the host immune system as extensively reviewed (Pickard *et al.* 2017).

Mucin glycosylation and associated bacteria in the gut

Mucin glycans make up ~80% of the molecular mass of mucins, the main structural component of mucus. Mucin-type O-glycosylation is initiated by a large family of polypeptide GalNAc transferases (ppGalNAc Ts) that add α -GalNAc to the Ser and Thr residues of peptides. Mucin glycosylation is characterized by a high degree of structural diversity which is based on three elements. The first is the type of core structure. There are eight mucin core structures in humans with structures 1–4 most commonly found in intestinal mucins (Tailford *et al.* 2015a; Thomsson *et al.* 2012; Brockhausen *et al.* 2009). The second stage of glycan diversity is determined by the action of a range of glycosyltransferases that elongate the mucin core through the addition of galactose, N-acetylgalactosamine (GalNAc) and/or N-acetylglucosamine (GlcNAc) residues leading to linear or branched chains of up to 20 residues (Gunning *et al.* 2013). The third element of diversity is conferred by the peripheral epitopes that are often fucosylated, sialylated or sulphated (Tailford *et al.* 2015a).

At the ecological level, the diversity of mucin glycans along the GI tract contributes to shape the structure and function of the gut microbiota. While the luminal microbiota may respond primarily to diet, the mucus-associated microbiota is influenced more directly by host-related factors. Importantly, the ability to utilize host mucin glycans as a carbon source gives bacteria a sustainable and consistent nutrient supply and a competitive advantage to colonize the mucus layer (Marcobal *et al.* 2013). As reviewed in Tailford *et al.* (2015a), it is now established that mucin glycan degradation is widespread across the major phyla represented in the human gut microbiota. *Akkermansia muciniphila* is a mucin glycan degradation specialist and, therefore, considered as a keystone member of the mucus-associated microbiota (Shin *et al.* 2019) while Bacteroidetes are viewed as general glycan degraders able to switch from dietary to host glycan metabolism due to their extensive array of carbohydrate-active enzymes (Ndeh and Gilbert 2018). Actinobacteria, which are largely represented by *Bifidobacteria* in the human gut microbiota, are typically adapted to carbohydrates with a low degree of polymerization and mucin glycan metabolism strategy is similar to the Firmicutes (Ndeh and Gilbert 2018). Consistent with this, the presence of mucins in *in vitro* fermentation models leads to an increased proportion of *Bacteroidetes*, *Akkermansia* and *Lachnospiraceae* species that are known mucin glycan degraders, whilst levels of *Lactobacillus* and *Bifidobacterium* decrease (Tran *et al.* 2016). *In vivo*, both chronic and intermittent fiber deficiency promotes enrichment of mucin glycan degrading bacteria in mouse models, leading to a significant increase in *A. muciniphila* and *Bacteroides caccae* species accompanied by a decrease of the fiber-degrading species (Desai *et al.* 2016).

Mucin glycan degradation strategies by gut commensal bacteria

Microbes most adept at mucin glycan degradation often encode sulfatases, deacetylases, sialidases and fucosidases to remove terminal structures and grant greater accessibility to the extended core structures (Etienne-Mesmin *et al.* 2019; Ndeh and Gilbert 2018). The monosaccharides freed by the action of these enzymes may be utilized by the bacteria themselves or released in the environment for scavenging bacteria (Marcobal *et al.* 2013). Furthermore, *in silico* analysis revealed that up to 86% of the human gut microbiota encode genes for cleavage of mucin glycans, with 89% encoding genes for the metabolism of the monosaccharides released (Ravcheev and Thiele

2017). The current model for mucin glycan degradation by the gut microbiota involves the sequential action of a number of glycoside hydrolases (GHs) (www.cazy.org; Figure 1) (Lombard *et al.* 2014).

Sulfate residues terminate mucin glycans and have been proposed to prevent GHs from removing terminal sugars, thus preventing the breakdown of mucin glycans (Etienne-Mesmin *et al.* 2019). In addition, the release of sulfate residues has been proposed to increase the levels of sulfate-reducing bacteria in the gut, leading to the production of H₂S, which can disrupt the mucus network and lead to epithelial damage (Praharaaj *et al.* 2018; Ijssennagger *et al.* 2016). Mucin-desulfating enzymes have been characterized primarily from the *Bacteroides* genus, with examples from *B. fragilis* and *B. thetaiotaomicron* (Praharaaj *et al.* 2018; Cartmell *et al.*, 2017). Recent work identified a *B. fragilis* sulfatase that was shown to be essential for growth on mucus *in vitro* and robust mucosal colonization *in vivo* (Donaldson *et al.*, 2020).

Exo-acting GHs are then involved in the trimming of terminal sugars from the O-glycan mucin chains, starting with the removal of fucose and sialic acid residues capping the GI mucin chains.

Fucose release involves fucosidases belonging to GH29 and GH95 families (www.cazy.org). GH95 enzymes functionally characterized so far show strict substrate specificity to the terminal Fuc α 1–2Gal linkage and hydrolyse the linkage *via* an inverting mechanism whereas GH29 enzymes show relatively relaxed substrate specificities with hydrolysis proceeding *via* a retaining mechanism (www.cazy.org). Fucosidases are found among numerous members of the gut microbiota, and often multiple fucosidases are found within a single genome, for example *Bifidobacterium bifidum* (Ashida *et al.*, 2009), *Bifidobacterium longum* (Garrido *et al.*, 2016; Bunesova *et al.* 2016), *Ruminococcus gnavus* (Croft *et al.* 2013) or *A. muciniphila* (Ottman *et al.* 2017). In these species, transcriptomics studies demonstrated that fucosidases were upregulated during growth on mucins, supporting their role in mucin glycan breakdown and utilization (Shin *et al.* 2019; Croft *et al.* 2016). Fucose metabolism has also been demonstrated for *B. thetaiotaomicron* and can trigger host fucosylation which *B. thetaiotaomicron* then uses as a nutrient source (Pickard and Chervonsky 2015). Fucose and mucin cross-feeding initiated by *B. bifidum* enables growth of *Eubacterium hallii*, an early occurring commensal species that produces butyrate and propionate from fermentation metabolites but that cannot degrade complex oligo- and polysaccharides (Bunesova *et al.* 2018; Schwab *et al.* 2017). However, not all fucosidases are extracellular, for example, 3 intracellular fucosidases with varying substrate specificities toward disaccharides have been characterized from lactobacilli (AlfA, AlfB and AlfC) (Rodríguez-Díaz *et al.* 2011), suggesting that Lactobacilli may import fucosyl-oligosaccharides.

Sialic residues are another highly sought-after source of nutrient terminating mucin glycan chains. The sialic acids comprise a family of 9-carbon sugar acids found predominantly on cell surface glycans of humans and other animals, the most common form of sialic acid in humans is N-acetylneuraminic acid (Neu5Ac). To access this carbon and nitrogen source, intestinal bacteria (both gut symbionts and pathogens) express GH33 sialidases (also known as neuraminidases), which cleave terminal sialic acid residues. Several sialidases have been functionally and structurally characterized from gut bacteria including species of Clostridia (Navarro *et al.* 2018) and Bacteroidetes, such as *Bacteroides fragilis* or *Bacteroides thetaiotaomicron* (Juge *et al.* 2016), as well as specific strains of *Bifidobacterium* (Nishiyama *et al.* 2018), *R. gnavus* (Tailford *et al.* 2015b) and *A. muciniphila* (Huang *et al.* 2015a). *B. fragilis* sialidase preferentially cleaves the sialyl α 2,8 linkage compared to sialyl α 2,3 and α 2,6 linkages that

similarity to GH101 members; however, they have a distinct substrate specificity, favoring the GalNAc- α 1-Ser Tn antigen structure found in mucin glycoproteins. They are abundant among *Bifidobacteria* species and act intracellularly suggesting transport of Tn antigen containing oligosaccharides in the bacteria (Kiyohara *et al.* 2012). The first crystal structure from the GH129 family showed structural similarities with GH101 but differences in substrate recognition account for the altered substrate specificity (Sato *et al.* 2017).

In *Bacteroides*, oligosaccharides are imported in the periplasm where they are further degraded, and the enzymes to do this are physically linked into loci termed polysaccharide utilization loci (PULs) (Brown and Koropatkin 2020, Lap  bie *et al.* 2019). In addition to the exo-acting GHs reported above and consistent with the glycan degradation strategy in these species, recent studies reported endo-acting enzymes that target the polyLacNAc structures within oligosaccharide side chains of mucins. These O-glycanases are found in several *Bacteroides* spp. as well as *A. muciniphila* and are a part of the GH16 family (Crouch *et al.* 2019). In addition, a high throughput screening approach led to the identification of novel GH31 and GH109 enzymes with α -GalNAcase activity (Rahfeld *et al.* 2019). These enzymes were found to have distinct specificities toward mucin-type O-glycans and blood type A-antigens. The α -GalNAcase GH31 enzymes act solely upon the GalNAc present in core structures of mucin-type O-glycans with no activity toward blood type A-antigens. The putative PULs in which the described α -GalNAcase GH31 enzymes are located showed no similarity to known mucin-degrading PULs (Rahfeld *et al.* 2019). Despite the well-known adaptations of certain *Bacteroides* spp. for degradation of mucosal glycans, they lack the GH101 or GH129 family enzymes that are used by other gut bacteria in host glycan degradation (Marcobal *et al.* 2013). Thus, these recently discovered GH31 activities with homologues found in PULs within other *Bacteroides*, highlight a potential means for more complete degradation of mucosal glycans by *Bacteroides* spp.

Perspectives

With the field of gut microbiota expanding beyond association studies and the increasing acknowledgment of the role of mucus-associated bacteria in human health, it is critical to continue our effort to gain mechanistic insights into the mechanisms underpinning microbial degradation of host mucin glycans. A full integration of glycomics in the field of microbiome research is warranted to further our understanding of the function and adaptation of microbial communities within the distinct nutritional niches in the gut. Combined with relevant *in vivo* humanized mouse models and advanced biopsy-based *in vitro* organ cultures, this biochemical knowledge will help to provide tangible molecular leads for developing therapeutic strategies to modulate the gut microbiota at the mucosa surface and strengthen gut barrier function in humans. Together, these targeted and omics approaches will potentiate the translation of microbiome research for biomarker development and precision medicine.

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