

Membrane mucins of the intestine at a glance

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ABSTRACT

Membrane mucins cover most mucosal surfaces throughout the human body. The intestine harbors complex population of microorganisms (the microbiota) and numerous exogenous molecules that can harm the epithelium. In the colon, where the microbial burden is high, a mucus barrier forms the first line of defense by keeping bacteria away from the epithelial cells. In the small intestine where the mucus layer is less organized, microbes are kept at bay by peristalsis and antimicrobial peptides. Additionally, a dense glycocalyx consisting of extended and heavily glycosylated membrane mucins covers the surface of enterocytes. Whereas many aspects of mucosal barriers are being discovered, the function of membrane mucins remains a largely overlooked topic, mainly

because we lack the necessary reagents and experimental animal models to investigate these large glycoproteins. In this Cell Science at a Glance article and accompanying poster, we highlight central concepts of membrane mucin biology and the role of membrane mucins as integral components of intestinal mucosal barriers. We also present the current consensus concerning the role of membrane mucins in host–microbe interactions. Moreover, we discuss how regulatory circuits that govern membrane mucins in the healthy gut display strong overlap with pathways that are perturbed during chronic inflammation. Finally, we review how dysregulation of intestinal membrane mucins may contribute to human diseases, such as inflammation and cancer.

KEY WORDS: Barrier, Glycocalyx, Intestine, Microvilli, Mucus, Mucin

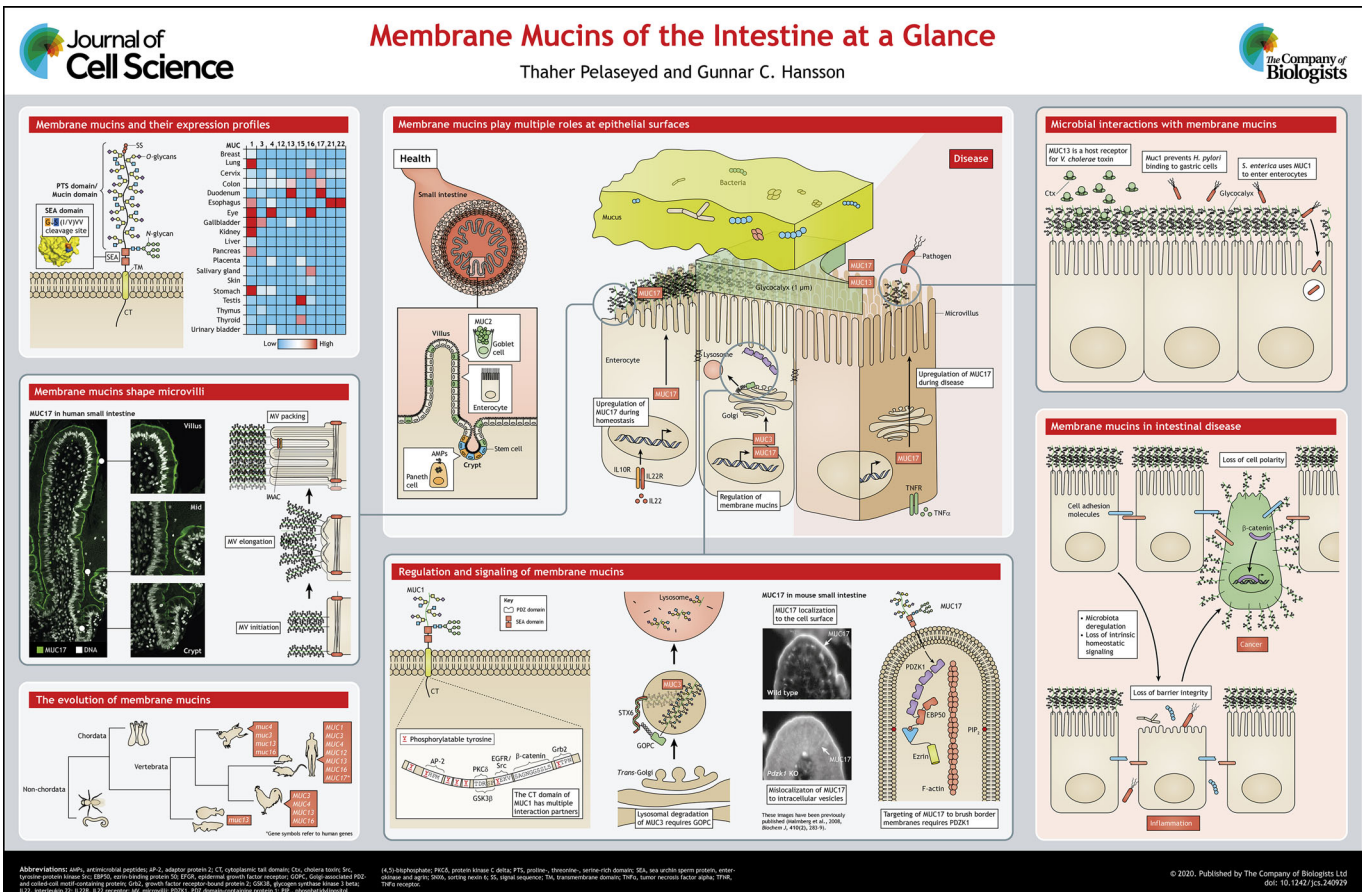
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Introduction

Membrane mucins are large and extended glycoproteins that are attached to the cell membrane through a single-pass transmembrane domain. The family of membrane mucins constitutes MUC1, MUC3, MUC4, MUC12, MUC13, MUC15, MUC16, MUC17,



MUC21 and MUC22 (see poster and Table 1). Membrane mucins are expressed at all mucosal surfaces, such as the eye, lungs and the gastrointestinal tract and in reproductive organs like the cervix but, here, we will mostly focus on those expressed in the intestine (see poster).

General features of membrane mucins

Membrane mucins are characterized by a specific domain with multiple and repetitive amino acid sequences rich in Pro, Thr and Ser residues, i.e. the PTS domain. Within this domain amino acids Thr and Ser are extensively *O*-glycosylated as the membrane mucin travels through the secretory pathway (Lang et al., 2007). The *O*-glycosylated proline-, threonine- and serine-rich (PTS) domain forms the typical mucin domain that is also a characteristic feature of secreted mucins, such as MUC2, MUC5AC, MUC5B and MUC6. All membrane mucins, except MUC4, MUC21 and MUC22, hold a sea urchin sperm protein, enterokinase and agrin (SEA) domain in their extracellular region (see poster). MUC4 is an interesting exception to the other membrane mucins because it has an extracellular domain assembly comprising three unique domains. These are the (i) nidogen (NIDO) domain, the (ii) adhesion-associated domain in MUC4 and other proteins (AMOP) domain, and the (iii) von Willebrand factor type D (vWD) domain. This configuration is only found in the sushi domain-containing 2 (Susd2) protein. Susd2 lacks a PTS domain (Duraisamy et al., 2006) and has homologs in frog as well as invertebrates, such as *C. elegans* and *D. melanogaster*. See text Box 1 for the evolutionary origins of membrane mucins.

The SEA domain of membrane mucins is autocatalytically cleaved at a G/S[I/V]VV consensus sequence during protein folding in the endoplasmic reticulum (ER) (Ligtenberg et al., 1992). The cleaved SEA domain is folded into a globular structure formed by four α -helices that cradle four parallel β -sheets, held together by strong non-covalent forces that are resistant to thermal and chemical denaturation (Macao et al., 2006; Pelaseyed et al., 2013b). When a SEA domain-containing membrane mucin finally reaches the

plasma membrane, it is a heteromeric glycoprotein comprising a long, heavily *O*-glycosylated extracellular fragment that is non-covalently linked through the SEA domain to a shorter fragment containing a transmembrane domain and a cytoplasmic tail domain.

The function of the conserved SEA domain is currently unknown. Notch receptors that mediate intercellular signaling harbor an extracellular domain called the negative regulatory region (NRR), which shares high structural homology with canonical SEA domains found in membrane mucins. However, the NRR domain lacks the characteristic autoproteolytic G/S[V/I]VV cleavage site (Gordon et al., 2009; Pei and Grishin, 2017). Instead, NRR adopts an autoinhibited conformation that conceals a proteolytic cleavage site that is revealed once Notch binds its ligand on an opposing cell, resulting in cleavage of Notch through a disintegrin and metalloprotease (ADAM) proteases and in subsequent signaling (Gordon et al., 2015). Mechanical forces can induce cleavage through ADAM proteases in the NRR, which is in line with findings showing that the SEA domain of MUC1 unfolds in response to mechanical forces (Pelaseyed et al., 2013b). In mouse, the endogenous ADAM17 protease can also act directly on membrane mucins. MUC1, for example, is cleaved by ADAM17 on the surface of uterine epithelial cells to allow embryo implantation (Thathiah et al., 2003).

MUC4 has a cleavage site located between Asp and Pro in the Gly–Asp–Pro–His (GDPH) sequence within the vWD domain that is typical for von Willebrand factor-derived proteins (Lidell et al., 2003). The cleavage of GDPH takes place in the ER but is probably autocatalytic and protease independent (Soto et al., 2006). Interestingly, the vWD domain is also found in secreted mucins, such as MUC2, MUC5AC and MUC5B, with MUC2 and MUC5AC having an autocatalytically cleaved GDPH motif (Ambort et al., 2012; Ridley et al., 2014; Trillo-Muyo et al., 2018). One of the vWD domains in these mucins mediates their oligomerization, suggesting that membrane mucins with a vWD domain participate in interactions with secreted mucins.

The SEA domain-containing membrane mucins MUC1, MUC3, MUC12, MUC13, MUC16 and MUC17 display a common domain organization, i.e. an extracellular fragment starting with an N-terminal signal sequence (SS) is followed by a PTS and SEA domain. A transmembrane domain is then followed by a cytoplasmic tail (CT) domain (see poster). MUC1, MUC3, MUC13 and MUC17 also contain EGF-like domains that flank the SEA domain on the extracellular fragment (Parry et al., 2001; Williams et al., 2001; Gum et al., 2002; Duraisamy et al., 2006). It has been suggested that EGF-like domains of membrane mucins function as ligands that can activate EGF receptor signaling (Carraway et al., 1999).

The fact that all surface membrane mucins are cleaved, non-covalently attached heteromers is intriguing and not yet fully understood. Membrane mucins cover epithelial surfaces that are subjected to environmental insults, suggesting that membrane mucins can simply shed their mucin domains to protect against biochemical and mechanical factors that, otherwise, might disrupt the epithelial monolayer. After shedding, the remaining membrane-attached mucin fragment could participate in intracellular signaling through specific intracellular motifs and sequences.

Glycosylation of membrane mucins

One of the hallmark features of mucins is glycosylation. Membrane mucins comprise PTS domains, in which >80% of all Ser and Thr residues carry *O*-linked glycans (see poster). Here, MUC17 serves as an example with its 4073 amino acid-long PTS domain with >2000 Thr and Ser residues, resulting in >1600

Box 1. The evolution of membrane mucins

The evolutionary origins of mucins cannot be traced by merely exploring genomes of organisms for the characteristic PTS domain, as amino acid sequences of PTS domains are poorly conserved between species. The characteristic trademark of mucins lies, instead, in the frequency of Pro, Thr and Ser residues within long, often recurring sequences or tandem repeats (Lang et al., 2004). Additional domains, such as AMOP, SEA and vWD, have also been looked at when investigating exon sequences in different organisms for the existence of membrane mucins (Lang et al., 2007). Whereas SEA domains are found in *Drosophila melanogaster* and *Caenorhabditis elegans*, SEA domain-containing proteins with a PTS domain emerged first in vertebrates, such as frog (*Xenopus tropicalis*) and zebrafish (*Danio rerio*) (Lang et al., 2007). Orthologues of the human *MUC1* gene are found among mammals, but *MUC1* is not present in other vertebrates, such as chick, frog or fish (see poster) (Spicer et al., 1995). Human *MUC3*, *MUC12* and *MUC17* are clustered in tandem on human chromosome locus 7q22. Most likely, this locus, with its three membrane mucin genes and their corresponding exon-intron organizations, is conserved from human down to frog (Lang et al., 2007). In analogy with the human 7q22 locus, the locus comprising murine *Muc17* is flanked by those of the acetylcholinesterase *Ache* and the E3 ubiquitin-protein ligase *Trim56*. This also supports the existence of *Muc3* and *Muc12* in mouse, in which they have not yet been fully sequenced (Lang et al., 2007). *MUC17* paralogs have been identified in opossum and *MUC17*-like proteins are expressed in zebrafish (Lang et al., 2007). The NIDO–vWD–AMOP domains of *MUC4* appeared first in *Xenopus* through fusion with a characteristic N-terminal PTS domain.

Table 1. Expression of transmembrane mucin in epithelial tissues

Protein	Tissue location	References
MUC1	Ocular surface, lung, mammary gland, stomach, kidney, female reproductive tract, gallbladder, immune cells	Uhlén et al., 2005; Govindarajan and Gipson, 2010; Johansson and Hansson, 2016
MUC3	Small intestine, colon	Uhlén et al., 2005; Johansson and Hansson, 2016
MUC4	Ocular surface, lacrimal glands, oral cavity, salivary glands, lung, mammary gland, stomach, colon	Uhlén et al., 2005; Govindarajan and Gipson, 2010; Johansson and Hansson, 2016
MUC12	Colon, rectum	Uhlén et al., 2005; Johansson and Hansson, 2016
MUC13	Small intestine, colon, rectum	Uhlén et al., 2005; Johansson and Hansson, 2016
MUC15	Thyroid, kidney, urinary bladder, female reproductive tract, placenta, colon	Uhlén et al., 2005; Johansson and Hansson, 2016
MUC16	Ocular surface, lung, female reproductive tract	Uhlén et al., 2005; Govindarajan and Gipson, 2010; Johansson and Hansson, 2016
MUC17	Small intestine, colon	Uhlén et al., 2005; Johansson and Hansson, 2016
MUC21	Esophagus, thymus, lung, skin, cervix, colon	Uhlén et al., 2005; Johansson and Hansson, 2016
MUC22	Esophagus	Uhlén et al., 2005; Johansson and Hansson, 2016

O-glycosylation sites. *O*-glycosylation is initiated by addition of *N*-acetylgalactosamine (GalNAc) to Ser or Thr residues, followed by stepwise extension of this first epitope into more-complex and branched glycan chains that forces the long membrane mucin protein to adopt the extended and linear conformation that is often evident in electron micrographs (Ito, 1965). The dense glycan chains also protect the protein backbone from digestive enzymes and microbial proteases (van der Post et al., 2013; Bergstrom et al., 2017). In addition, *O*-glycosylation has been reported to regulate apical targeting of membrane mucins (Kinlough et al., 2011).

Most membrane mucins also carry several *N*-linked glycans on Asn residues. MUC17 carries nine Asn residues flanking the extracellular SEA domain, which potentially undergo *N*-glycosylation. *N*-glycosylation occurs in the lumen of the ER, and is required for correct folding and export of membrane mucins through interactions with mannose-binding lectin chaperones in the ER. Impaired *N*-glycosylation in the ER results in protein misfolding followed by degradation (Lamriben et al., 2016).

There are regional differences in glycosylation caused by selective and differential expression of glycosyltransferases along the digestive tract, and differences between healthy or diseased states (Robbe et al., 2003; Holmen-Larsson et al., 2013; Johansson et al., 2015). Microbiota also induce expression of glycosyltransferases, such as sialyltransferases, as shown when comparing glycosyltransferase expression and *O*-glycosylation of mucins between germ-free and conventional microbiota-harboring mice (Johansson et al., 2015; Arike et al., 2017). Microbial regulation of host protein glycosylation is crucial for the etiology of intestinal disease, such as inflammatory bowel disease (IBD), the collective term for Crohn's disease and ulcerative colitis. There, altered bacterial communities affect MUC2 glycosylation and may decimate its capacity to act as a barrier protecting the epithelium (Larsson et al., 2011). These external and intrinsic regulatory processes can also affect glycosylation of membrane mucins expressed along the length of the intestine.

The interactome of membrane mucins

The CT domains of membrane mucins hold sequences and motifs involved in protein interaction, targeting and signaling through phosphorylation. The CT domain of MUC1 contains several conserved Ser, Thr and Tyr phosphorylation sites that modulate interactions with various binding partners (Spicer et al., 1995; Schroeder et al., 2001; Wang et al., 2003; Singh et al., 2007). For example, the proto-oncogene tyrosine-protein kinase Src, the members of the epidermal growth factor receptor (EGFR) ErbB2 and ErbB3, glycogen synthase kinase 3 beta (GSK3 β) and protein

kinase C δ (PKC δ), all interact with MUC1, together with other partners that lack kinase activity, such as adaptor protein complex 2 (AP-2), β -catenin and growth factor receptor-bound protein 2 (Grb2) (Kinlough et al., 2004; Funes et al., 2006; Singh and Hollingsworth, 2006). MUC3, MUC12 and MUC17 contain class I PDZ binding motifs, i.e. x[S/T] ϕ (where x represents any amino acid and ϕ indicates any hydrophobic amino acid) in their cytoplasmic tail domains, making them ligands for PDZ domain-containing proteins involved in assembly of protein and signaling complexes (Malmberg et al., 2008). MUC3 interacts with the *trans*-Golgi-resident PDZ protein Golgi-associated PDZ and coiled-coil motif-containing protein (GOPC, also known as CAL) and functions as a part of a larger protein complex that consists of the Q-SNARE protein syntaxin 6 (STX6) and the small GTPase Rho-related GTP-binding protein RhoQ (RHOQ, also known as TC10). Together, they mediate cargo trafficking from the *trans*-Golgi to the lysosome for degradation (Cheng et al., 2010) (see poster). Another target for GOPC-facilitated degradation is the cystic fibrosis transmembrane conductance regulator (CFTR) anion channel that transports bicarbonate and fluids into the gut lumen to unfold mucus (Gustafsson et al., 2012). Overexpression of either MUC3 or CFTR rescues either of these GOPC-binding partners from lysosomal degradation, demonstrating a direct link between membrane mucins and CFTR function in epithelial cells with yet unknown consequences (Pelaseyed and Hansson, 2011). MUC17 binds to three out of four PDZ domains in PDZ domain-containing protein 1 (PDZK1) that organizes protein complexes, as exemplified by PDZK1 augmenting CFTR channel activity by assembling dimers of the anion channel (Wang et al., 2000). Mouse MUC17, which normally resides at the apical membrane of small intestinal enterocytes, localizes to intracellular vesicles in *Pdzk1* knockout mice (*Pdzk1* KO), suggesting that PDZK1 regulates apical targeting or retention of MUC17 at the plasma membrane (Malmberg et al., 2008). Intriguingly, cholinergic stimulation of cultured epithelial cells or mouse duodenal cells results in activation of the CFTR and its relocalization to the apical membrane, alongside removal of MUC17 from apical surfaces followed by colocalization with PDZK1 (Pelaseyed et al., 2013a). The CT domain of human MUC17 contains two phosphorylation sites that are conserved in the mouse MUC17; however, the consequence of MUC17 phosphorylation is not yet understood (Schneider et al., 2019). Interaction between membrane mucins and multivalent PDZ proteins supports the idea that membrane mucins are components of regulated protein complexes, including ion channels, cytoskeletal proteins and regulatory kinases, which act in concert in response to stimuli. The diversity of membrane mucin interaction partners

testifies to the fact that membrane mucins have important biological functions at mucosal surfaces, as discussed below.

Membrane mucins of the intestines

In humans, the intestinal tract constitutes the largest surface area that is in contact with the harsh environment of the outside world. Our intestines are lined with a rapidly renewing monolayer of epithelial cells, which is turned over every three to five days (Cheng and Leblond, 1974). Valuable intestinal stem cells at the base of intestinal crypts differentiate into specialized epithelial lineages that, collectively, contribute to mucosal barriers against chemical and microbial challenges. Therein, intestinal stem cells (ISCs) differentiate into specialized epithelial lineages that, collectively, contribute to mucosal barriers against chemical and microbial challenges. Paneth cells within the small intestine secrete antimicrobial peptides that safeguard the neighboring stem cells. Goblet cells produce, store and secrete mucus that protects epithelial surfaces (Johansson et al., 2008; Vaishnava et al., 2008). Transporting epithelial cells – termed enterocytes in the small intestine and colonocytes in the colon – account for 70–80% of all intestinal epithelial cells, and participate in nutrient uptake and ion exchange. Enterocytes are characterized by their apical brush border membrane, shaped by ~1000 microvilli that cover the surface of each cell. Each microvillus is 1–2 μm long, has a diameter of 100–150 nm and is capped with extended membrane mucins that are likely to be the main glycoprotein component of the glycocalyx (see poster). This morphological term was first used and described in the late 1950s for the surface of red blood cells (Bartlett, 1958). The glycocalyx that decorates the surface of intestinal epithelial cells was first observed in bat and later in cat intestines (Ito and Winchester, 1963; Ito, 1965).

The role of membrane mucins in shaping apical membrane domains

Membrane mucin MUC17 is highly expressed in the small intestine, whereas expression levels are lower in the colon (Uhlén et al., 2015). Recent advances in single-cell RNA sequencing of mouse small intestine show that MUC17 is almost exclusively expressed in enterocytes, with lowest levels in progenitor enterocytes and highest in mature differentiated enterocytes (Haber et al., 2017). The distinct spatiotemporal expression pattern of MUC17 is shared with a cluster of proteins, such as *Cdhr2*, *Cdhr5*, *Ebp50*, *Ezrin* and *Ush1c* (see poster). These proteins are responsible for assembly, elongation and formation of stable bundles of packed microvilli that are, in turn, decorated with membrane mucins. Microvilli are evolutionarily conserved actin-based membrane protrusions that shape the membrane of enterocytes by generating a brush border membrane (see poster on how membrane mucins shape microvilli) (Pelaseyed and Bretscher, 2018). The cellular cues that initiate microvilli formation have not yet been defined but it is known that microvilli assembly requires: (i) actin cytoskeleton treadmill towards the tip of the microvillus (Meenderink and Tyska, 2019), (ii) continuous cycles of phosphorylation and dephosphorylation of ezrin – a crosslinker between the membrane and F-actin cytoskeleton; a process that, in turn, requires phosphatidylinositol (4,5)-bisphosphate (PIP₂) and an ezrin-specific kinase to assemble microvilli (Viswanatha et al., 2012; Pelaseyed et al., 2017) (see poster). Assembled microvilli are then tightly packed via an inter-microvillar adhesion complex (IMAC) that comprises *Cdhr2*, *Cdhr5*, *Myo7b* and *Ush1c*, an ensemble of proteins that form stable crosslinks between microvilli (Crawley et al., 2014). Once stable packing of microvilli through the adhesion complex occurs, membrane mucins are likely to be locked in place at the tip of

microvilli until the cell is shed. The stable retention of the glycocalyx has been shown by using *in vivo* labeling of surface glycoproteins covering enterocytes (Schneider et al., 2018).

The correlation between MUC17 and microvillar components, and the fact that each microvillus is decorated with a certain number of membrane mucins, suggest a functional association between membrane mucins and microvilli that is not yet fully understood. A recent publication suggests that the densely *O*-glycosylated domains of membrane mucins at the plasma membrane generate physical forces that bend the membranes to form microvillar protrusions (Shurer et al., 2019).

The brush border membrane of enterocytes constitutes a crucial interface with the gut lumen. The fact that this surface is covered with membrane mucins alludes to their function in host–microbe interactions. To determine how membrane mucin expression and microvillar architecture are interconnected will be crucial in order to understand how epithelial barriers contribute to intestinal homeostasis.

Microbial interactions with membrane mucins

The gut lumen harbors trillions of microorganisms that contribute to our well-being by priming our immune system, promoting intestinal maturation, extracting nutrients from ingested food and generating metabolites that are important for intestinal homeostasis (Ley et al., 2005). Membrane mucins present dense arrays of glycans to the luminal content of the gut. On one hand, the numerous multivalent glycan moieties in the mucin domain of membrane mucins offer excellent stoichiometric power to allow specific interactions with glycan-binding proteins of gut microbes. On the other hand, membrane mucins decorate the tip of microvilli and form a thick carbohydrate-rich coat that may act as a highly specific barrier based on charge, chain length and branching of mucin glycans. Another possibility is that membrane mucins act as binding and attachment sites for bacteria (see poster). Thus, in a combined binding and barrier function, membrane mucins can act as decoys that limit microbial binding to cells surfaces. This has been shown for murine MUC1 that is highly expressed in the gastric epithelium; there, it limits acute and chronic *Helicobacter pylori* colonization by preventing *H. pylori* from binding directly to enterocytes (McGuckin et al., 2007). In another study, oral infection of mice with *Campylobacter jejuni* upregulated protein levels of MUC1 along the gastrointestinal tract and, in turn, suppressed the pro-apoptotic action of the *C. jejuni* toxin, explaining why the bacterium induces epithelial damage and translocates systemically in *Muc1*^{-/-} mice (McAuley et al., 2007). Studies of *in vitro* cancer cell cultures have also suggested that *Salmonella enterica* strains invade epithelial cells by binding to sialylated MUC1 through their giant adhesin SiiE (Li et al., 2019). Human MUC13 has been identified as a host receptor for the pentameric B-subunit of *Vibrio cholerae* toxin (Ctx) in human T84 cells; however, whether MUC13 is an entry route or a protective decoy for Ctx has not yet been explored (Wands et al., 2015). Recently, we showed that overexpression of MUC17 in a 2D human epithelial Caco-2 cell culture with low endogenous MUC17 expression reduced binding of enteropathogenic *Escherichia coli* (EPEC) to cell surfaces in a TNF-dependent manner (Schneider et al., 2019), supporting the concept that membrane mucins function as cell-autonomous barriers against bacteria (see poster).

Regulation of membrane mucins in health and disease

Several membrane mucins show aberrant expression in cancers. MUC1 overexpression in colon, gall bladder and pancreas cancers often correlates with metastasis and poor prognosis (Nakamori

et al., 1994; Hiraga et al., 1998; Kashiwagi et al., 2000; Lüttges et al., 2002). Moreover, epigenetic changes, such as DNA methylation and histone acetylation, have been shown to upregulate MUC4 and MUC17 in pancreatic cancer (Vincent et al., 2008; Kitamoto et al., 2011). Although the role of membrane mucins in cancer is not fully understood, several mechanisms have been suggested. Loss of regulated cell polarity and dissociation of cancer cells from neighboring cells has been attributed to the heavily glycosylated mucin domain (Maher et al., 2011) (see poster). Overexpression of MUC1 has also been shown to both mediate and block cell–cell adhesion due to interactions between its mucin domain and proteins, such as selectins and intracellular adhesion molecule 1 (ICAM1) (McDermott et al., 2001). Moreover, the CT domain of MUC1 engages several binding partners, such as β -catenin, that are known to be involved in carcinogenesis (see poster).

How external signals and intrinsic programs regulate membrane mucins in health and disease is only beginning to be understood. Insight into the signaling pathways that govern membrane mucins can be gained by investigating human diseases, such as inflammatory bowel disease (IBD), and mouse models of acute enteropathogenic infections. In the mouse colon, *in vivo* interleukin 22 (IL22) upregulates gene expression of *Muc1*, *Muc13* and *Muc17* (Sugimoto et al., 2008). IL22 and interferon gamma (IFN γ) also upregulates *Muc17* in organoids derived from mouse small intestine but not in those from colon (Price et al., 2018). IL22 is a homeostatic interleukin involved in epithelial cell regeneration and barrier reinforcement (Sanos et al., 2009). Together with its downstream signaling pathway components, such as the transcription factor signal transducer and activator of transcription 3 (STAT3), *IL22* has been identified as a susceptibility gene in IBD (Glocker et al., 2009; Silverberg et al., 2009; Khor et al., 2011; Chi et al., 2014). Indeed, an earlier study has reported that the membrane mucin genes *MUC1*, *MUC4*, *MUC12*, *MUC13* and *MUC17* are downregulated in humans suffering from Crohn's disease (CD) or ulcerative colitis (Moehle et al., 2006). A more-recent study has reported abnormal microvillar morphology in CD patients, and correlated this observation to the significant downregulation of genes involved in microvillus assembly and maintenance in CD patients as compared to the control group (VanDussen et al., 2018). An intriguing explanation for the role of membrane mucins in IBD is that perturbations in membrane mucin expression and microvillar assembly can result in defective glycocalyx, leading to loss of epithelial barrier integrity.

Conclusions and future perspectives

Membrane mucins are a neglected family of membrane-bound glycoproteins that cover many epithelial surfaces of the human body. In this Cell Science at a Glance article and poster, we have discussed structure, function, glycosylation and microbial interactions of membrane mucins, particularly, in the intestinal tract. However, many crucial gaps of knowledge remain to be addressed. What is the fundamental role of membrane mucins in epithelial cells? Do membrane mucins act as receptors for specific bacteria or as specialized barriers against pathogens? How are these large glycoproteins trafficked to the cell surface and how are the spatiotemporal dynamics of membrane mucins coordinated with cell differentiation in tissue with a high cell turnover? At various sites through the human body, two or more membrane mucins are expressed in the same cell type. How are these membrane mucins connected in terms of localization and function? Finally, the comprehensive scrutiny of regulatory pathways that dictate gene

expression of membrane mucins will add another layer of understanding regarding infectious and inflammatory diseases in the intestine.

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