Mucin 2 and unfolded protein response reshape the mucus barrier in inflammatory bowel disease (Review)

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Abstract. Mucin 2 (MUC2) is the primary structural component of the intestinal mucus layer and is essential for maintaining the integrity of the mucus barrier and influencing the development of inflammatory bowel disease (IBD). Disruption of MUC2 production or secretion compromises barrier function, increasing susceptibility to the chronic mucosal inflammation characteristic of IBD. Given their large size and complex folding requirements, immature MUC2 precursors easily accumulate in the endoplasmic reticulum (ER) and cause ER stress, leading to activation of the unfolded protein response (UPR). The UPR restores ER homeostasis by reducing protein synthesis, enhancing folding, and degrading misfolded proteins. The mammalian UPR has three known signaling branches: Pancreatic ER kinase, ER transmembrane inositol-requiring enzymes 1α and β (IRE1α and IRE1β) and activating transcription factor 6. Anterior gradient 2 (AGR2) is a dimeric protein disulfide isomerase family member involved in the regulation of protein quality control in the ER. Importantly, IRE1β-AGR2 signaling potentially serves as a superior regulatory mechanism for controlling UPR activation caused by the misfolding of MUC2 in goblet cells. The present review highlights the critical role of MUC2 dysfunction and UPR imbalance in IBD pathogenesis. Targeting the association between novel UPR signaling pathways and restoring MUC2 protein function may provide new insights into IBD research and treatment.

Contents

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1. Introduction

Inflammatory bowel disease (IBD) is a type of noninfectious chronic gastrointestinal inflammation disease that includes Crohn's disease (CD) and ulcerative colitis (UC) and is characterized by chronic or intermittent inflammation of the intestinal mucosa (1). Globally, in 2019, 405,000 (95% UI 361,000 to 457,000) new cases of IBD and 41,000 (95% UI 35,000 to 45,000) deaths from IBD have been reported (2). It is projected that the age-standardized mortality rate from IBD may continue to decline from 2020 to 2050 (2). The results of clinical trials have indicated primary non-response rates of up to 40%, and a significant challenge is the inability to predict which treatment will benefit individual patients (3). The investigation of preclinical human IBD mechanisms is one of the key concerns (4).

The mucus layer of the intestines is the first interface to insulate the complex microbial environment, and the integrity of the mucus layer directly affects intestinal barrier function and the development of IBD (5). Mucus is a dilute, aqueous and viscoelastic secretion that contains 90-95% water, 1-2% lipids, electrolytes, 29 core proteins and other substances; mucins are the primary structural and functional components in mucus and are present at concentrations of 1-5% (6). Mucus separates the epithelium and millions of antigens from food, the environment and the microbiome while permitting nutrient absorption and gas exchange (7).

Goblet cells secrete large polymers of gel-forming mucin 2 (MUC2), which compose the structural backbone of the mucus that coats the epithelial surface (8). The MUC2 mucus barrier plays important roles in the response to changes in dietary patterns, MUC2 mucus barrier dysfunction, contact stimulation with colonic epithelial cells, and mucosal and submucosal inflammation during the occurrence and development of IBD (9,10). MUC2 gene expression is reduced or absent in patients with CD, whereas MUC2 protein expression and secretion are decreased in active UC, resulting in a thin mucus layer and increased intestinal absorption (11).

The absence of MUC2 expression in the mucus layer renders animals vulnerable to intestinal inflammation, which leads to the development of spontaneous colitis and predisposes them to the development of colorectal cancer (12). MUC2-knockout mice present clinical signs of colitis along with mucosal thickening, increased proliferation, and superficial erosion (13).

MUC2 dysfunction and endoplasmic reticulum (ER) stress often occur in IBD (14). When there is a defect in the synthesis and processing of proteins and disturbances in calcium levels or redox states in goblet cells, the accumulation of unfolded/misfolded proteins within the ER leads to ER stress (15). MUC2 precursors accumulate in the goblet cells of patients with UC, and even the non-inflamed intestinal tissues of these patients show signs of ER stress (16). Altered MUC2 synthesis and, consequently, aberrant MUC2 assembly induce ER stress and promote colonic inflammation in mice (17). Under ER stress conditions, signaling pathways that are collectively termed the unfolded protein response (UPR) are activated to restore the ER to its physiological state (18). Appropriate UPR may reduce the accumulation of MUC2 precursors in the ER, facilitating the proper folding of MUC2 and exerting a therapeutic effect in the early stages of IBD (19).

The present review aimed to explore the importance of MUC2 in the mucus barrier and the novel UPR pathway to provide new ideas for future research on IBD.

2. Mucus barrier is dominated by MUC2

The human MUC gene family encodes 19 typical mucin-type glycoproteins, which are recognized by the Human Genome Organization Gene Nomenclature Committee (http://www.genenames.org) and can be divided into three subgroups, membrane-bound (including MUC1, MUC3A and MUC3B), secreted gel-forming (including MUC2, MUC5AC and MUC5B) and secreted non-gel-forming (MUC7 and MUC8) (Table I). Among these, MUC2 is the most important secreted and gel-forming component of the intestinal mucus in the human intestine and provides a first line of defense against pathogens in the gut immune system (20).

Structure of MUC2. MUC2 is the first human secretory mucin to be identified and characterized (21). The major building block of colonic mucus is MUC2, a glycoprotein consisting of ~5,200 amino acids and ~80% glycans, mostly O-glycans (22). The MUC2 protein has three von Willebrand D domains (VWD), a VWD' domain (lack of an E module compared with VWD), a central high frequency of hydroxy-amino acids (Ser and Thr) together with a Pro (PTS) sequence interrupted by two CysD domains and a C-terminal with VWCN (a globular structure with a VWC fold), one VWD and three von Willebrand C domains (VWC) with a VWC' domain (half of a C domain compared with VWC) followed by a cystine-knot (CK) domain (Fig. 1A) (23). Membrane-tethered and secreted non-gel-forming mucins do not contain these important polymerizing domains, such as VWD and PTS, and thus do not form gels (24).

Cysteine residues located at the N- and C-termini of MUC2 are highly glycosylated, which increases the hydrophilicity of MUC2 and allows lubrication of the intestinal mucosa (25). MUC2 contains 215 cysteine amino acids that make up >10% of the total amino acids outside the PTS mucin domains (26). As all cysteines need to be interlinked (oxidized) to exit the ER, the correct assembly of MUC2 is a formidable challenge (26). A MUC2 monomer contains up to 1,600 O-glycans and 30 N-glycans, resulting in more than 3,300 terminal sugar residues (27).

MUC2 synthesis and modification. MUC2 monomers are N-glycosylated within the ER, a process that enables correct MUC2 folding, stable dimer formation and maturation (22). The CK domain in the C-terminus of MUC2 forms a dimer via disulfide bonds between three cysteine amino acids via the ER machinery (Fig. 1B) (28). The correct folding of MUC2 is assisted by various molecular chaperones that prevent the misfolding and aggregation of proteins in the ER, such as binding immunoglobulin protein (BiP, GRP78), anterior gradient 2 (AGR2), calnexin and calreticulin (29).

Next, MUC2 dimers are transported to the Golgi, and the hydroxy amino acids (Ser and Thr) of the PTS domains become O-glycosylated, in which >80% of all Ser and Thr residues carry O-linked glycans (30). The typically O-glycosylated compounds are largely concentrated in the PTS domains, which resemble bottle brushes with protein cores at their centers and oligosaccharides as their bristles (31). In the trans-Golgi network, the glycosylated dimers are then trimerized via disulfide bonding in VWD3, and a net-like structure is generated (Fig. 1B) (32). The glycosylated MUC2 monomer has a mass of ~2.5 MDa and the polymer may have a mass of >100 MDa (33). An important function of O-glycans is to cover the protein backbone and thus protect the mucin from proteolytic enzymes while simultaneously binding water to generate a gel (33). Glycans also act as attachment sites for bacteria, as they are important food sources (34). An increase in the number of small glycans is found in most patients with active UC, and a decrease in the number of more complex compounds has been detected (31).

The distribution of glycosyltransferases (GalNAc-Ts) throughout the Golgi apparatus is not homogenous, and each compartment has a distinct composition of GalNAc-Ts (35). To achieve controlled, sequential extension, the GalNAc-Ts are spatially arranged according to the order of monosaccharide addition (27). First, O-glycosylation is a covalent linkage initiated by 1 of the 20 GalNAc-Ts that add N-acetylgalactosamine (GalNAc) to the Ser or Thr amino acid residues in the MUC2 PTS sequence (36). The Pro amino acids in the PTS ensure a non-folded structure allowing the GalNAc-Ts of the Golgi apparatus to access the protein core (37). The structures formed during this initial stage of modification are known as Tn antigens. Next, the glucan chains are further extended to form four core structures known as Core 1-4 (Fig. 1C) (38). The addition of galactose (Gal) by Core 1 β1-3-galactosyltransferase (C1GalT1) is known as core 1 (39). The addition of N-acetylglucosamine (GlcNAc) by Core 3 β1-3-N-acetylglucosaminyltransferase (β3GnT6) to peptide-bound GalNAc is known as Core 3 (40). Core 2 is formed by the addition of β1-6GlcNAc to the GalNAcs of Core 1 through Core 2 β1,6-N-acetylglucosaminyltransferase 1/3 (C2GnT1/3) (41). Core 4 is formed by the addition of β1-6GlcNAc to the GalNAc of Core 3 through Core 2 β1,6-N-acetylglucosaminyltransferase-2 (C2GnT2) (38). Groups that can be attached to core structures

Table I. Mucin protein specificity in human tissue.

A, Membrane-bound

Mucin	HGNC ID	Chromosome	Protein expression
MUC1	7508	1q22	Cytoplasmic and membranous expression mainly in glandular cells and respiratory epithelial cells
MUC3A	7513	7q22.1	Not available
MUC3B	13384	7q22.1	Heart
MUC4	7514	3q29	Cytoplasmic and membranous expression in respiratory epithelia, glandular cells in the gastrointestinal tract, cervix and prostate
MUC12	7510	7q22.1	Luminal expression in the colon and rectum
MUC13	7511	3q21.2	Distinct cytoplasmic and membranous expression in the gastrointestinal tract
MUC15	14956	11p14.2	Membranous expression in several tissues, including the epididymis, salivary and thyroid glands, placentae and seminal vesicles
MUC16	15582	19p13.2	Cytoplasmic and membranous expression in glandular cells of the cervix, endometrium, fallopian tubes, salivary glands and respiratory epithelium
MUC17	16800	7q22.1	Luminal membranous expression in the small intestine
MUC20	23282	3q29	Low tissue specificity
MUC21	21661	6p21.33	Membranous expression in the squamous epithelia of the esophagus, vagina and cervix
MUC22	39755	6p21.33	Not available

B, Secreted gel-forming

Mucin	HGNC ID	Chromosome	Protein expression
MUC2	7512	11p15.5	Selective expression in the mucus-producing cells of the gastrointestinal tract
MUC5AC	7515	11p15.5	Selective expression in the mucus-producing cells of the stomach, respiratory epithelium, cervix and gallbladder
MUC5B	7516	11p15.5	Selective expression in the mucus-producing cells
MUC6	7517	11p15.5	Distinct cytoplasmic expression in the stomach, seminal vesicles and gallbladder
MUC19, oligomeric	14362	12q12	Salivary gland, testis

C, Secreted non-gel-forming

Mucin	HGNC ID	Chromosome	Protein expression
MUC7	7518	4q13.3	High and selective expression in the salivary glands
MUC8	7519	12q24.33	Tracheobronchial

Data were collected from http://www.genenames.org, https://www.proteinatlas.org and https://www.genecards.org. HGNC, Human Genome Organization Gene Nomenclature Committee.

include galactose, sialic acid, sulfate and fucose (42). The order in which the glycans interact with different GalNAc-Ts plays a critical role in O-glycosylation since specific monosaccharides, such as fucose or N-acetylneuraminic acid, can limit further elongation (27). There are large differences in MUC2 characteristics between animal species, such as mouse colonic MUC2, which largely contains Core 2 and minor amounts of Core 3 and Core 4, whereas human MUC2 predominantly contains Core 3 structures, Core 4 to a lesser extent, and essentially lacks Core 1 (42).

Formation of the MUC2 network. MUC2 forms large net-like structures that are densely packed in the secretory granules of goblet cells (43). Fully synthesized MUC2 is released from goblet cells through baseline secretion or via Ca^{2+}-dependent stimulated secretion (44). The pH along the secretory pathway shifts gradually from 7.2 in the ER to 6.0 in the trans-Golgi network, and to 5.2 in the secretory granule (45). Moreover, the intragranular Ca^{2+} concentration increases, suggesting that the packing of MUC2 may be pH- and Ca^{2+}-dependent (45). The N-terminal trimers spontaneously form concatenated rings

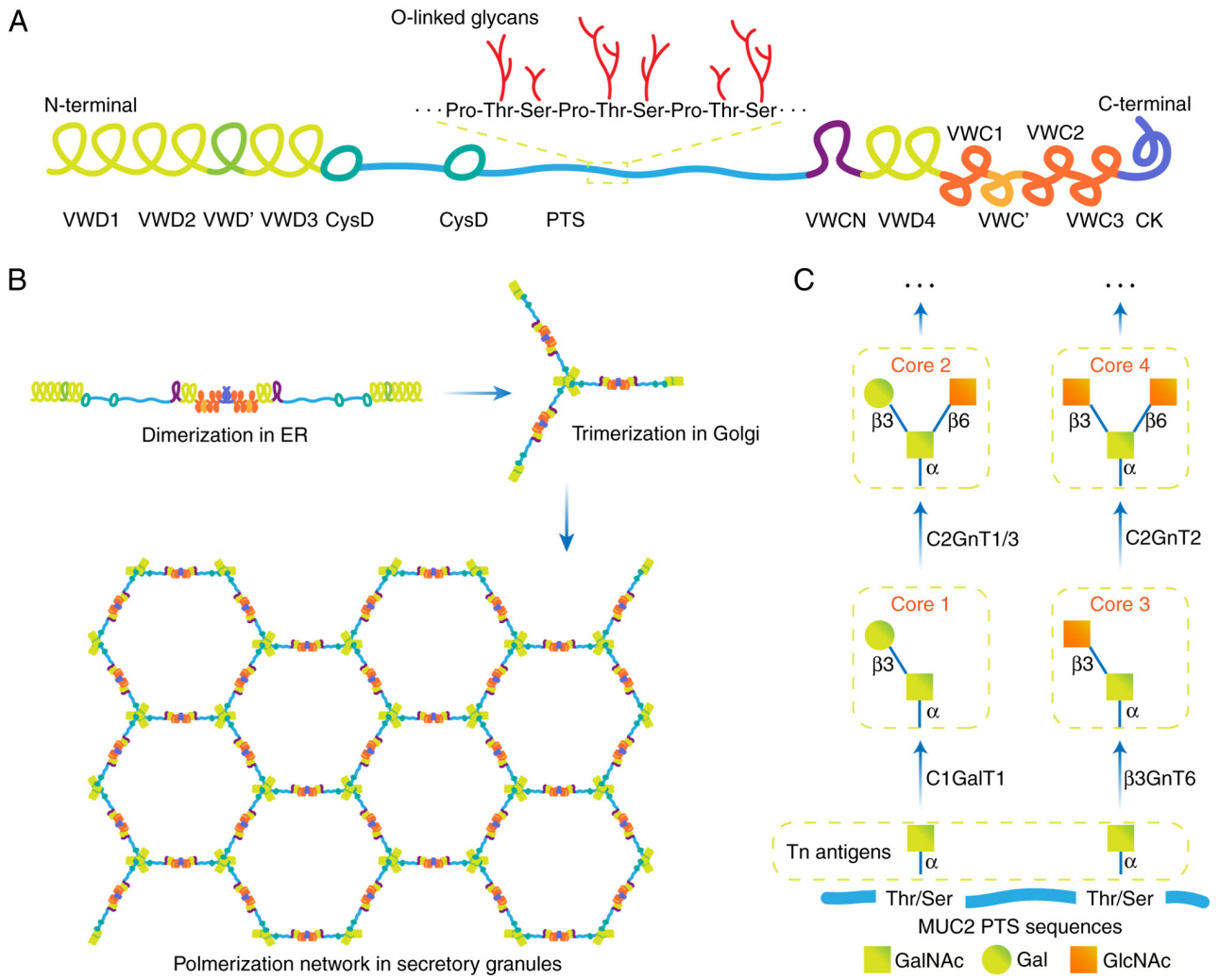

Figure 1. Domain structure and biosynthesis of MUC2. (A) Diagrammatic representation of MUC2. (B) Assembly of the MUC2 mucin into dimeric forms in the ER, and the formation of trimeric forms in the Golgi network. (C) Common mucin-type O-glycosylation Core 1-4 biosynthetic pathways. Each oligosaccharide can be extended by various glycosyltransferases and sulfotransferases to generate various O-glycan structures. MUC2, mucin 2; ER, endoplasmic reticulum; VWD, von Willebrand D domains; CK, cystine-knot; GalNAc, N-acetylgalactosamine.

with long-extended mucin domains standing perpendicular to this structure and joining to other MUC2 molecules end-to-end through their C-terminus (46).

After secretion, the expression of Na^+/H^+ exchanger 3 (NHE3), the dominant isoform of the apically expressed Na^+/H^+ exchangers at the surface of epithelial cells contributes to an acidic mucosal milieu (47). NHE3 transports luminal sodium in exchange for cellular hydrogen and helps facilitate a pH gradient at the brush border as hydrogen diffuses out of the unstirred layer (10). The mucus is then converted to a more voluminous, loose outer mucus layer with increasing pH and removal of N-terminus-bound single calcium ions (10). Upon secretion, the densely packed mucin expands >1,000-fold into a large net (48). In general, the outer layer is twice as thick as the inner layer (49). The inner mucus layer forms a barrier impervious to bacteria and thus protects the colonic epithelium, which is essentially sterile (30).

In addition, the hydrolytic activities of some proteases also play a role in the process of MUC2 volume expansion (50). Calcium-activated chloride channel regulator 1 is highly abundant in intestinal mucus, with an N-terminal metalloprotease domain, a central von Willebrand A domain and a C-terminal fibronectin type III domain that likely has both metallohydrolase activity and structural roles and can process N-terminal MUC2 via proteolysis (51). Transglutaminase 3, the dominant cross-linking enzyme in the mouse colon, catalyzes cross-linking of the MUC2 protein and increases the resistance of MUC2 to degradation (52). Under the synergistic effects of numerous factors, MUC2 forms a net-like structure and establishes a sturdy mucus barrier.

3. MUC2 dysfunction and ER stress are intertwined in the pathogenesis of IBD

In response to environmental factors, such as pathogenic bacterial infection, there is an increased demand for MUC2 synthesis, resulting in a significant protein folding and modification burden on the ER of goblet cells (53). Additionally, owing to the large size (~2.5 MDa of a monomer) and complex structure of MUC2, it is prone to misfolding, which may result in the accumulation of misfolded proteins within the ER lumen, thereby triggering ER stress (54). Abnormal synthesis

of MUC2 induces a unique model of IBD caused by ER stress (55). In the Winnie and Eeyore mouse models (which carry single missense MUC2 mutations), misfolded MUC2 proteins heavily accumulate in membranous structures, and quantitative PCR reveals a two- to threefold increase in the expression of BiP mRNA (an ER stress marker) in the proximal and distal colon (16). Winnie and Eeyore mice develop mild spontaneous inflammation of the colon accompanied by goblet cell ER stress (16). Winnie mice exhibit altered mucus production as early as 4 weeks of age, after which colonic inflammation begins (56).

ER stress aggravates MUC2 synthesis abnormalities and causes a series of chain reactions (57). The synthesis of MUC2 begins in the ER, where it must be properly folded and bound to a molecular chaperone before it can be transported to the Golgi apparatus (58). Once abnormal MUC2 folding occurs, it is difficult to perform glycosylation, sulfation and other modifications, which are performed in the Golgi apparatus, leading to further functional defects in MUC2 (31). For example, the O-glycosylation patterns of MUC2 are significantly altered in patients with IBD, especially in patients with UC; these patterns include O-glycosylation reduction, a reduction in the length of the O-glycan chains of MUC2 and genetic defects in GalNAc-Ts enzymes (59). Sulfation is catalyzed mainly by sulfotransferases located in the Golgi apparatus, and sulfotransferase adds sulfuric acid groups to the sugar chains of MUC2, resulting in the formation of negatively charged molecules whose hydration and viscosity properties are increased (11). Since the presence of a sugar chain is necessary for sulfation, the obstruction of MUC2 glycosylation reduces the number of sulfation sites, thus affecting the addition and distribution of sulfuric acid groups and resulting in changes in the charge and viscosity properties of MUC2 (60). Moreover, delayed transport or misfolding of MUC2 due to ER stress can affect the recognition sites of proteolytic enzymes, resulting in the failure of MUC2 to undergo proper hydrolysis and extracellular secretion of MUC2, further impairing intestinal barrier function (61).

4. ER homeostasis depends on the UPR balance

UPR signaling pathways are activated to stop improper translation, refold unfolded proteins, and degrade irreversible unfolded proteins via the ER-associated degradation (ERAD) pathway, in which unfolded/misfolded proteins that have accumulated in the ER are transported to the cytosol for degradation by the ubiquitin-proteasome system (62). UPR sensors monitor ER protein folding capacity, and their effectors balance protein synthesis, folding, trafficking, and degradation to alleviate ER stress (62). The mammalian UPR has three known signaling branches: Pancreatic ER kinase (PERK), ER transmembrane inositol-requiring enzymes 1α and β (IRE1α and IRE1β) and activating transcription factor 6 (ATF6) (Fig. 2). These transmembrane sensor proteins have an ER luminal sensor domain and a cytosolic effector domain, thereby transmitting the protein folding status inside the ER to other cellular compartments via intracellular signaling pathways (63). In the absence of misfolded proteins in the ER lumen, these cascades are usually maintained in an inactivated state by the chaperone BiP (64). However, under elevated ER stress, unfolded proteins compete for BiP binding, thereby detaching BiP from the sensing molecules, which activates the signaling cascade to overcome the stress environment and sustain homeostasis (64). Moreover, under protracted and acute ER stress, the UPR initiates cascades that can trigger apoptosis in goblet cells, which are essential for the production of MUC2 (65). Thus, maintaining the balance of the UPR is very important.

IRE1 pathway. IRE1 proteins, which include IRE1α and IRE1β, possess both an ER luminal sensor domain and a cytosolic endoribonuclease (RNase) domain and show kinase activity (66). Kinase activity enables trans-autophosphorylation, which activates RNase activity (67). Activated IRE1 splices X-Box Binding Protein 1 (XBP1) mRNA and removes an inhibitory 26-nucleotide intron from the XBP1 transcript (68). The mRNA is subsequently re-ligated by RNA terminal phosphorylase B, generating a functionally active isoform of XBP1 (XBP1s) (69). XBP1s bind to ER stress response element (ERSE), ER stress response element II (ERSE II) and UPR element sequences (70). This process upregulates the expression of genes that encode proteins that promote protein refolding (ER chaperone proteins), aid in the destruction of proteins that are beyond repair (components of the ERAD machinery) and encode proteins that facilitate the expansion of the ER, thus increasing protein folding capacity (71). In addition to splicing XBP1, IRE1 RNase activity can cleave other RNA targets in a process known as regulated IRE1-dependent decay (72).

PERK pathway. PERK is a transmembrane protein located in the ER, and its N-terminal regulatory motif is located in the lumen and adjoins the cytosolic eIF2α kinase domain (73). PERK is maintained in an inactive state by the interaction of its ER luminal domain with BiP (74). Once a misfolded protein is produced, BiP dissociates from PERK due to its preferential binding to hydrophobic residues of misfolded proteins (75). Once disassociated, following phosphorylation at Thr980 by autophosphorylation, PERK dimerizes to form an active homodimer (76). The activation of PERK leads to the phosphorylation of eukaryotic initiation factor 2 (eIF2α) at Ser51 (77). Phosphorylated eIF2α perturbs 80S ribosome assembly inhibiting protein translation, thus blocking the production of an additional influx of nascent polypeptides that could worsen the ER stress (78).

Moreover, activating transcription factor 4 (ATF4) escapes translational attenuation by eIF2α phosphorylation because ATF4 has upstream open reading frames (ORFs) in its 5'-untranslated region (79). These upstream ORFs prevent translation of ATF4 under normal conditions and are bypassed only when eIF2α is phosphorylated; therefore, ATF4 translation occurs (80). ATF4 translation activates the expression of the transcription factor CCAAT/enhancer binding protein-homologous protein, a master regulator of ER stress-induced apoptosis and plays pro-apoptotic roles in the stress response (81). Chronic or prolonged PERK signaling can lead to goblet cell apoptosis in IBD (82).

ATF6 pathway. ATF6 proteins are type II transmembrane proteins that contain basic leucine zipper (bZIP) motifs in their

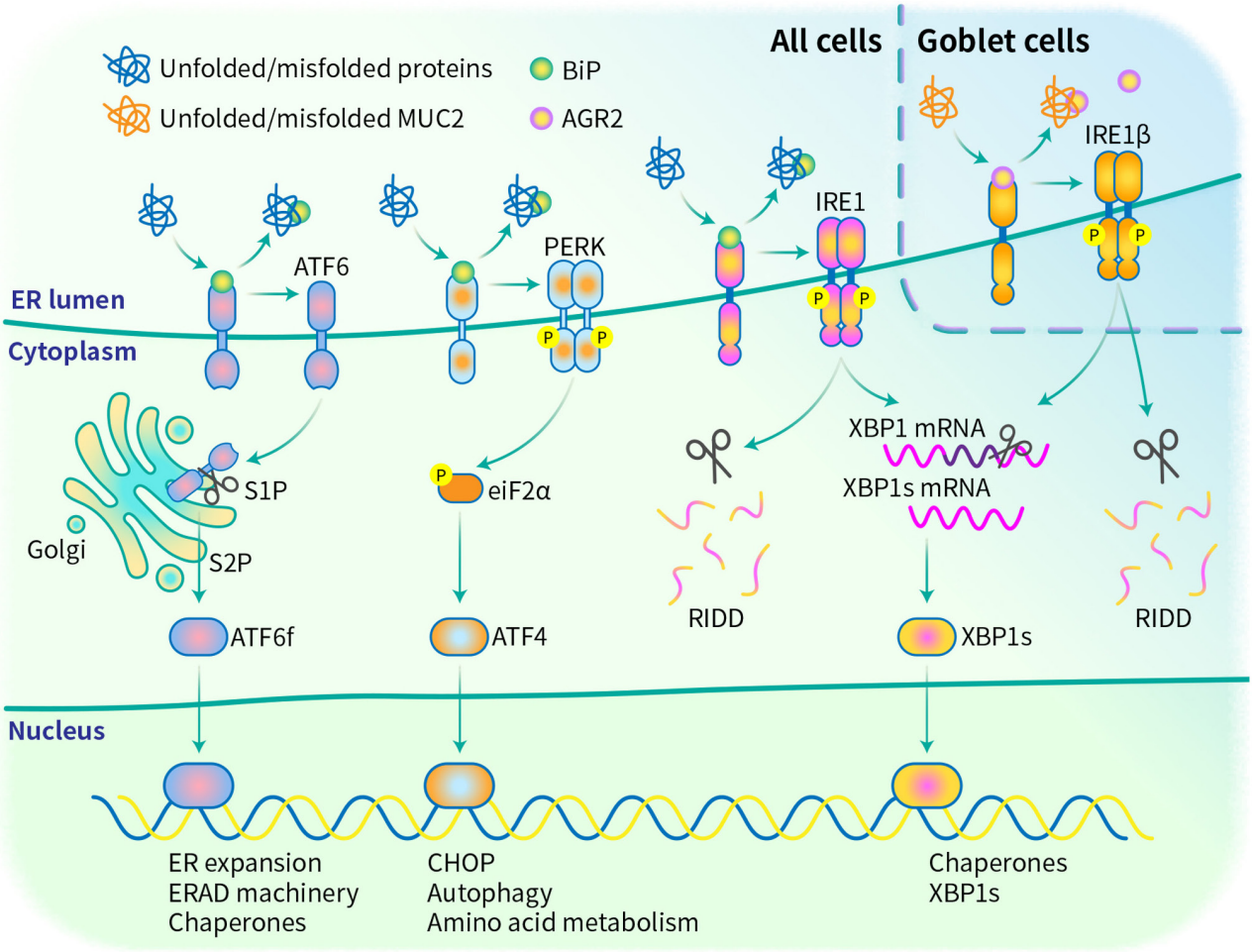

Figure 2. Major UPR pathways within the ER and UPR activation controlled by AGR2-IRE1β signaling caused by misfolded MUC2 in goblet cells. BiP senses the presence of misfolded proteins and releases ATF6, IRE1 and PERK to enter their active states, resulting in transcriptional programs that decrease ER stress. Goblet cells possess a relatively effective UPR sensor, IRE1β, whose activity is repressed by AGR2, a cell-specific chaperone, through a mechanism analogous to the repression of IRE1α by BiP. CHOP, CCAAT/enhancer binding protein-homologous protein, a master regulator of ER stress-induced apoptosis plays a pro-apoptotic role in the stress response. ER-associated degradation pathway transports accumulated unfolded/misfolded proteins from the ER to the cytosol for degradation by the ubiquitin-proteasome system. RIDD degrades mRNAs localized to the ER membrane through IRE1 RNase activity, thereby reducing the influx of proteins into the ER lumen. UPR, unfolded protein response; ER, endoplasmic reticulum; AGR2, anterior gradient 2; IRE1β, ER transmembrane inositol-requiring enzyme 1β; ATF6, activating transcription factor 6; PERK, pancreatic ER kinase; RIDD, regulated IRE1-dependent decay.

cytosolic domains and a C-terminus protrudes that into the ER lumen (83). After disassociation from BiP under ER/oxidative stress conditions, ATF6 translocates from the ER to the Golgi apparatus, where it is cleaved by site-1 protease (S1P) and site-2 protease (S2P) to remove the luminal and transmembrane domains (84). This process results in the generation of a cytosolic fragment with transcription factor activity which is designated as ATF6f, the released ATF6f then translocate to the nucleus and regulates the expression of genes encoding BiP, XBP1s and ERAD components (85).

IRE1β-AGR2 signaling potentially controls UPR activation caused by misfolded MUC2 in goblet cells. Unlike IRE1α, which plays a broad role in the UPR by splicing XBP1 mRNA and degrading misfolded proteins, IRE1β has specialized functions in secretory epithelial cells, especially in goblet cells (86). Vertebrates express two IRE1 paralogs, IRE1α, which is universally expressed and IRE1β, which is specifically expressed within mucus-secreting cells in the respiratory and gastrointestinal tracts (87). Single-cell RNA sequencing revealed that the abundance of IRE1β mRNAs is ~50-fold greater than that of IRE1α mRNAs in the goblet cells of the small intestinal epithelium (88). Loss of IRE1β expression results in the accumulation of misfolded MUC2 precursor proteins in the ER of immature goblet cells, and defects in MUC2 maturation and its accumulation in the ER lead to marked ER abnormalities and signs of ER stress (89).

The role of IRE1β in intestinal mucus barrier homeostasis can't be replaced by IRE1α (90). The transplantation of microbiota from conventionally raised mice to germ-free mice restored goblet cell numbers; this restoration was completely abolished in IRE1β-deficient mice, despite normal IRE1α expression, but it failed to compensate for IRE1β function (91). Compared with normal colonic tissues, the tumor tissues exhibited a significant increase in XBP1s mRNA expression levels, no significant difference in IRE1α mRNA expression, and a significant decrease in both IRE1β and MUC2 mRNA and protein levels (92). Moreover, the expression levels of 23 genes associated with the mechanistic target of rapamycin complex 1 signaling pathway were increased in the

IRE1β-knockout intestinal epithelial cells (IECs) compared with IRE1α knockout IECs in both an ER stress mouse model treated with tunicamycin, and a colitis mouse model induced by 2.5% DSS (93). These findings indicated that, unlike IRE1α, IRE1β exerts a novel non-canonical splicing target gene unique in IECs.

AGR2 selectively binds to IRE1β, but not IRE1α. AGR2, a member of the protein disulfide isomerase (PDI) family with redox and molecular chaperone functions that process and modify immature mucins into mature mucins, is highly expressed in goblet cells (94). AGR2 forms disulfide bonds with the N- and C-terminal cysteine-rich sections of MUC2 (94). Impaired AGR2 function, such as H117Y mutation and S-glutathiolation modification, directly suppresses MUC2 biosynthesis, inducing ER stress and driving IBD pathogenesis (58,95). Bio-Layer Interferometry revealed a half-maximal binding concentration of 19 μM for binding of the IRE1β luminal domain (LD) to AGR2, whereas an immobilized IRE1α LD resulted in significantly weaker binding signals with AGR2 (96). The interaction between IRE1β and AGR2 does not involve disulfide bonds, and AGR2 binding favors the formation of IRE1β LD monomers (96). Both the C81S and H117Y mutations in AGR2 abrogate its ability to bind and inhibit IRE1β activity (97). Importantly, both the N-terminus (residues 21-1,397) and the C-terminus (residues 4,198-6,178) of MUC2 have a derepression effect on the IRE1β-AGR2 pair, and the derepression effect on IRE1α is relatively weak under the same conditions (96).

These results suggest that the IRE1β-mediated UPR likely works by binding with AGR2 in a manner such as that of BiP and IRE1α, by antagonizing IRE1β LD dimerization (Fig. 2) (98). The IRE1β-AGR2 pathway may be an important UPR pathway in goblet cells.

5. Discussion

MUC2 dysfunction disrupts intestinal host-commensal homeostasis. An imbalance in host-microbiota interactions leading to a thinner mucus layer may be an early sign of IBD (99). The exposed terminal glycans on the outer surface of MUC2 can be recognized by bacteria and lectins, providing adhesion binding sites for intestinal commensal bacteria and utilizing mucin O-glycans as an energy source (27). *Escherichia coli* secretes the metalloprotease SslE, *Vibrio cholerae* secretes the metalloprotease TagA, and *Candida albicans* secretes the aspartyl protease Sap2, which can all degrade mucins, potentially allowing microbial penetration of the mucosal barrier (100). Decreased MUC2 expression induced by REGγ gene deficiency in goblet cells leads to dysregulation of the intestinal flora (101). ST6GalNAc1 (ST6)-mediated sialylation protects MUC2 from bacterial proteolytic (such as protease of C1 esterase inhibitor and O-glycoprotease) degradation to maintain mucus integrity, and ST6 R319Q mutation mice harbor a different microbiome with less diversity (102).

MUC2 dysfunction leads to an imbalance in the extracellular matrix (ECM), resulting in ECM remodeling, and further exacerbating intestinal fibrosis in IBD. The ECM forms a complex network of multidomain macromolecules composed of collagen, elastin, fibronectin, laminin, aminoglycans and proteoglycans (103). ECM provides structural support to IECs while cooperatively establishing intestinal barrier function with the mucus layer (103). Upon disruption of the mucus barrier, bacterial products such as lipopolysaccharides recruit neutrophils, which release MMPs and elastase, leading to excessive degradation of ECM components including elastin, collagen, fibronectin, and proteoglycans (104). Although probiotics generally have beneficial effects, there is a risk that probiotics (such as *Bacteroides fragilis* and *Lactobacillus gasseri*) may degrade the ECM components abundant in either the mucosa or submucosa (collagen I and IV, laminin, fibronectin and hyaluronic acid) and exacerbate inflammation (105).

Although appropriate UPR have beneficial effects, chronic and aberrant UPR aggravates ECM remodeling, which in turn exacerbates MUC2 dysfunction. The IRE1α/XBP1 arm of the UPR upregulates the expression of integrins, laminins, collagens, MMP1, MMP10 and MMP9 in epithelial cells, which further leads to the remodeling of the basement membrane (106). Excessive degradation of the ECM may inhibit the differentiation of intestinal stem cells into goblet cells by increasing yes-associated protein 1 (YAP)-dependent signaling, thereby reducing the MUC2 synthesis (107,108). Moreover, excessive proinflammatory cytokines such as tumor necrosis factor α and interleukin 13 produced in the ECM upregulate MUC2 mRNA synthesis, which increases the metabolic load on intestinal cells and causes ER stress in IECs (109,110).

The development of artificial mucus layer and small-molecule drugs targeting the UPR signaling pathway have shown efficacy in IBD. An artificial mucus layer formed from a thiol-substituted hyaluronic acid derivative excellent protection against the penetration of *Escherichia coli* (111). Epithelial cell ER-targeted protein, a recombinant variant of the cholera toxin B subunit, induces colon epithelial mucosal healing in colitis by activating the IRE1α/XBP1 arm of the UPR in colon epithelial cells (112,113). Integrated stress response inhibitor, a small molecule inhibitor of the UPR, blocks eIF2α phosphorylation and PERK pathway activation, thereby preserving intestinal epithelial integrity in IBD by mitigating aberrant apoptosis (114). The development of small-molecule drugs targeting the IRE1β-AGR2-MUC2 axis of the UPR in goblet cells and further elucidating the functional distinctions between IRE1α and IRE1β may provide new strategies for mucosal healing in IBD.

The effects of UPR signaling pathways are intricate and interconnected and involve both positive and negative effects. The present review emphasizes the positive impact of the UPR on the synthesis of MUC2 in early-IBD. But its negative effects, such as the induction of apoptosis and ECM remodeling, cannot be ignored. Focusing solely on isolated aspects of mucus layer function yields limited understanding, research and therapeutic strategies should adopt a holistic approach.

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Authors' contributions

ZWY and FZ designed and supervised the review. ZX, LYL and JZX conducted literature organization and revised the review. ZWY contributed to draft the manuscript. ZWY and FZ reviewed this manuscript. All authors contributed to the manuscript and approved all aspects of the work. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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