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INTESTINAL MUCUS LAYER AND MUCINS (A REVIEW)

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ABSTRACT

The gastrointestinal tract, like the urinary, respiratory, reproductive tracts and the surface of the eye, has large surface areas which are in contact with the exterior environment. The mucosal tissues in the gastrointestinal tract are exposed to large number of exogenous, water or food born microbiota. Therefore, they serve as access routes for different types of bacteria, parasites, viruses, enzymes and toxins. In order to protect the mucosal tissues against pathogens and aggressive enzymes, which are necessary in digestive processes, they are covered by a resident microbial flora and also by a viscoelastic adherent mucous gel layer. The mucus layer acts as the first line of defense against threats and also as a positive environment for beneficial endogenous microbiota adapted for symbiotic living. The quantity and quality of mucus layers varies throughout the gastrointestinal tube and is often changed and disrupted during the occurrence disease. A disturbed mucus layer in the intestine can result in changes in the whole organism, such as: impaired immunity, loss of weight and weak food conversion, which is important, especially in food animals. That is why several researchers have focused on these changes, both in humans and other animals, to find out methods and countermeasures, which will facilitate the best protection for the mucus layer in the intestine. In this review, we describe the composition and function of the mucus layer and mucins in the intestine.

Key words: gastrointestinal tract; intestinal mucus layer; mucins

INTRODUCTION

The gastrointestinal tract is covered by a mucus layer, which is the product of secretory cells forming the inner layer of digestive tube (*tunica mucosa*), which is in contact with lumen. The mucus layer acts as a physical barrier, protecting the mucosal surface from dehydration and mechanical damage. It has an important role against destructive hydrolases, digestive enzymes, pathogenic bacteria, viruses and parasites and other chemical insults. By lubricating, it helps the passage of the digestive matter and creates an es-

sential and stable environment at the mucosal surface for the enteric microflora. The mucus layer has an important function with its selective permeability, which is adaptable and may be regulated in response to extracellular stimuli, such as nutrients, cytokines and bacteria. It may also affect the nutrient absorption by changing the permeability of small nutrients released by the activity of brush border digestive enzymes. The mucus layer protects the mucosal tissue against pathogens by inhibiting the binding sites for the bacterial adhesines, maintaining high concentrations of secreted IgA and lysozyme and acting as a free radical scavenger [8]. Normal intestinal mucosal epithelium has a tolerance to commensal microbiota because of its ability to distinguish them from pathogenic microorganisms by their molecular patterns, such as microbe associated molecular patterns and pathogenic-associated patterns, through pattern recognition receptors such as cell surface Toll-like receptors and cytoplasmic nucleotide-binding oligomerization domain like receptors [10].

MUCUS IN THE INTESTINE AND COLON

As mentioned in the introduction, mucus in the intestine and colon is produced by cells covering the *tunica mucosa*, which lies in contact with the lumen of the digestive tube and is built from four principal cells: enterocytes, enteroendocrine cells, Paneth cells and goblet cells. All these cells arise by mitosis from pluripotent stem cells located near the base of the crypts of Lieberkühn [12, 19]. The main producer of highly hydrated mucus cover in the gastrointestinal tract are goblet cells. These cells are cup-like shaped, containing segregated organelles and are in contact with the lumen. Although goblet cells are distributed throughout the entire length of the gastrointestinal tract, their contribution to the epithelial volume is not constant, so the thickness of the mucus layer is physiologically not the same in different parts of the intestine [25].

The mucus layer in the intestine and colon is comprised of water, ions, cytokines and molecules of the immune systems, such as: immunoglobulin A and anti-microbial peptides, defensins, protegrins, collectins, cathlecidins and histatins, which facilitate the clearance of pathogenic organisms [14, 27].

MUCINS

The viscosity of the mucus layer results from non–covalent interactions between large and highly hydrated glycoconjugates — mucins, which are also products of goblet cells synthetization. Mucus glycoproteins are polydisperse molecules, specific with their ability to carry out multiple tasks at the mucosal surface of the gastrointestinal tract and their antimicrobial activity. They consist of a protein backbone and a high proportion of O-linked carbohydrates. Commonly found monosaccharides in mucins are: N-acetylgalactosamine, N-acetylglucosamine, galactose, fructose and sialic acids. In small amounts, there can also be found N-linked mannose saccharide [26]. According to Corfield et al. [6], there are 13 mucin gene members, each with specific glycosylation and characteristic protein domains, divided into two basic groups: secreted, and membrane-associated. Linden et al. [16] divided mucins into three groups with 15 genes: secreted gel-forming mucins, cell-surface mucins, and secreted non-gel forming mucins. Cell-surface mucins are present on the apical membrane of all mucosal epithelial cells and provide a barrier to limit the access of large molecules and other cells to the cell surface. Secreted gel-forming mucins are major constituents of the mucus layer and provide its viscoelastic characteristics. They are the product of the cells in the epithelial surface or by glands in the *tela submucosa*. In the small intestine and colon can be found from secreted gel forming mucins, only MUC2 type, and from the cell-surface mucins: MUC1, MUC3A/B, MUC4, MUC12, MUC13, MUC15 and MUC17. Non-gel forming mucins are not present in the intestine or colon [13, 22]. Another division of mucin in the intestine is based on the affinity of mucin content to histological staining. Immature goblet cells of the intestinal neoplasms and foetal intestinal cells produce neutral, still incomplete mucin. Acid mucin is the product of mature, sulphomucin — containing Goblet cells. There can be found two types of acid mucin in the intestine: sulphomucins, and sialomucins. It is suggested, that acidic mucins are more resistant against microbiological degradation, than neutral mucins, because they appear to be less degradable by bacterial glycosidases and host proteases. It is known, that the synthesis of mucin and staining characteristics of mucins in goblet cells correlate with or lack of differentiation and maturity/immaturity of goblet cells through disease, especially in malignancy [1, 7, 24].

There are two mainly used histological methods for microscopic examination: formalin fixation followed by paraffin embedding and tissue freezing followed by embedding in cryo-protectant media. To detect neutral and acidic mucin in mucus, there is the use of Periodic Acid Schiff staining, and for the amount of only acid mucin in mucus layer, it is Alcian Blue staining [5]. As it is known, mucin can be secreted in three ways of secretion showed by surface mucous-secreting cells: single granule exocystis, apical expulsion or compound exocystis and cell exfoliation [9].

REGULATION OF MUCUS SECRETION

The regulation of mucus secretion is controlled by the neural, hormonal and paracrine system and also by the immune system. Under physiological conditions, without pathogens or other abusive elements, there is balance between the mucus secretion rate and its erosion through enzymatic digestion caused by luminal proteases and mechanical shear and removal by movement of luminal contents. This mechanism leads to relatively stable thicknesses of the adherent mucus layer [3]. If there is an influence of pathogens or other insults, there can be found alterations in goblet cells including their hyperplasia, increased mucin secretion, and changes in mucin glycosylation. In addition to other components of the host immune response, these changes lead to clearing of the infections [15]. Mucosal pathogens can penetrate not only the disrupted mucus layer, but they may also disregard the M cells, which are specifically designed to capture and present microbes to the underlying lymphoid tissue as a hole in the mucus barrier. The reason is because in the place of M cells, there is a lack of goblet cells, only a thin layer of mucus barrier and glycocalix, formed by glycoproteins and glycolipids. The average physiological thickness of the mucous layer is 700 μm. Destroyed thicknesses of the mucus layer is found in pathological states like: peptic ulcer disease, ulcerative colitis and infection by *Helicobacter pylori*, *Escherichia coli* and *Campylobacter jejuni* [11, 18, 21].

INTESTINAL ABSORPTION AND THE ROLE OF THE MUCUS LAYER

Knowledge about the role of the mucus layer is very important because of its influence on the whole organism, such as: protection against pathogens, good condition, nutrient absorption and connected food conversion, monitored and needed especially in farm animals, like chicken, pigs and cows kept for meal production. Intestinal absorption, means transport of substrates from the intestinal lumen through the mucus and epithelial layers into the blood and lymphatic system and its special function of the plasmatic membrane of enterocytes. Molecules can penetrate the lipid membrane by: simple passive diffusion, carrier – mediated diffusion, active transport or pinocytosis. To enlarge the surface on which absorption can occur, the intestinal lumen creates folds, villi and microvilli, which results in a 600 - fold increase of the surface area of the small intestine. Lipophilic substances pass through a lipid membrane normally faster than hydrophilic substances [4].

Polysaccharides cannot be absorbed in the intestine, only monosaccharides can, which are products of starch degradation or originated from dietary disaccharides. The specific enzymes of the brush border, which are necessary for saccharides absorption, are synthesized in maturing enterocytes and embedded in the apical membrane. Carbohydrates, which could not be resorbed in the small intestine because of malabsorption, poor digestion, intestinal hurry, or decreased intestinal surface lack of enzymes, will reach the colon and will be degraded by bacterial hydrolases. One role of the small intestine is the hydrolysis of food proteins to the molecules, which can be transported through the venous system. Protein assimilation occurs mainly in the distal jejunum and proximal ileum and has three phases: luminal phase, brush border membrane phase and cytoplasmatic phase [4]. The luminal phase consists of cleavage of polypeptides by pancreatic enzymes like trypsin, chymotrypsin, elastase and carboxypeptidase. The brush border membrane phase works on two mechanisms: brush border hydrolysis of oligopeptides and membrane translocation of small peptides. After intracellular intake, dipeptides in the cytoplasmatic phase are hydrolyzed to the amino acids and then reach the venous system. Fat is absorbed in the luminal and mucosal phase. During the luminal phase, fat from food are solubilized as micellar dispersions of monomeric lipids by the interaction of components of the upper gastrointestinal tract. In the mucosal phase, fatty acids, cholesterol and fat-soluble vitamins are transported through the jejunal mucosa into the blood [4].

Because the European Union implemented the ban on the use of antibiotics as antimicrobial growth promoters in

animal nutrition, various feed additives are researched for their efficiency to promote growth performance and health [2]. It has been determined, that the dietary administration of phytogenic feed additives, such as essential oils, oleoresins and flavonoids, affect broiler growth performance, nutrient utilization and caecal microflora composition [20). The effects of these probiotics has also been investigated. Probiotics such as *Lactobacillus planetarium* were reported to induce MUC2 and MUC3 and to inhibit the adherence of enteropathogenic *Escherichia coli*. Enhanced mucus layers and glycocalyx and occupied microbial binding sites by Lactobacillus sp. provided protection against invasion by the pathogens [17]. Several studies on newly hatched chicken have been done to find out, how nutrition can affect the mucin content. It has been determined, that food deprivation — starvation immediately after hatching caused delayed mucosa development and perturbed mucin dynamics. On the other hand, intra-anionic nutrient supply had a trophic effect on the chicken small intestine and enhanced goblet cell development [24]. The experiments mentioned above are only fragments from a number of other studies done, and are still in progress, on sheep, pigs, chicken and rats. All of these studies point to the necessity to continue more experiments focused on the protection of the mucus layer and its secretion and also on the influence of pathogens on mucus. The collection of results from different studies and comparison of them should lead to lower incidences of infectious diseases caused by enteropathogens, both in humans and other animals and to figure out the best countermeasures like probiotics and other nutritive additives against mechanical, chemical and biological insults. This should lead to increased health condition and taking on weight in meat animals and to the protection of gastrointestinal mucus layer in humans, who undergo long-time antibiotic treatment and are exposed to enteropathogens or parasites.

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