Effects of Mycotoxins on Intestinal Mucin and Their Mechanisms of Action: Postprint

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Abstract

Mycotoxins are secondary metabolites produced by molds during the field growth, harvest, storage, or processing of grains, and are widely present in feed ingredients and human food. Mycotoxins not only substantially reduce feed quality, but also severely impair animal health and decrease animal production performance; their residues in animal-derived products pose a serious threat to human health. Numerous studies have demonstrated that mycotoxins can disrupt the intestinal mucosal barrier, alter gut microbiota composition, modify intestinal immune responses, induce intestinal lesions, and cause intestinal inflammation. Mucins secreted by intestinal goblet cells constitute the primary component of the mucus layer—the first line of defense in intestinal innate immunity. Intestinal mucins play a crucial role in maintaining intestinal mucosal homeostasis and regulating microbe-host immune responses. This article reviews domestic and international research on the effects of mycotoxins on intestinal mucin production and its underlying mechanisms, providing a theoretical foundation for future in-depth studies in this field.

Full Text

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Abstract

Mycotoxins are secondary metabolites produced by fungi during the field growth, harvest, storage, or processing of cereals, and are widely present in feed ingredients and human food. Mycotoxins not only substantially reduce feed quality but also seriously compromise animal health and production performance, while their residues in animal products pose significant threats to human health. Numerous studies have demonstrated that mycotoxins damage the intestinal mucosal barrier, alter intestinal microbiota composition, modify intestinal immune responses, induce intestinal lesions, and trigger intestinal inflammation. Mucins secreted by intestinal goblet cells constitute the primary component of the mucus layer—the first line of defense in intestinal innate immunity. Intestinal mucins play a crucial role in maintaining intestinal mucosal homeostasis and regulating microbe-host immune interactions. This review synthesizes research findings from China and abroad to examine the effects of mycotoxins on intestinal mucin production and the underlying mechanisms, providing a theoretical foundation for future in-depth investigations in this field.

Keywords: mycotoxins; intestinal mucins; intestinal mucosal injury; regulatory mechanisms

Mycotoxins are natural biological contaminants primarily produced as secondary metabolites by filamentous fungi or molds [1]. Common mycotoxins include aflatoxin (AF), ochratoxin (OTA), deoxynivalenol (DON), fumonisin (FBs), zearalenone (ZEA), and nivalenol (NIV) [2]. These toxins contaminate feed and animal-derived foods (meat, eggs, milk, etc.), causing substantial harm to animal production performance and human health [3]. Notably, mycotoxin contamination of feed and food is typically mixed in nature. Toxic symptoms from feeding naturally contaminated mycotoxin feeds are often more severe than those from purified mycotoxins, due to interactive effects between two or more mycotoxins. The toxicity of multiple concurrent mycotoxins may manifest as additive, sub-additive, synergistic, potentiating, or antagonistic effects [4]. Mycotoxin residues first trigger innate immune responses (including secretion of pro- and anti-inflammatory cytokines) upon absorption, though these responses are often insufficient to completely eliminate the harmful agents [5-6]. As the primary organ defending against foreign contaminants, the intestine accounts for 70% of the body' s immune defense. When the intestinal mucosal barrier—the first biological line of defense—becomes dysfunctional, it not only induces intestinal inflammation but also significantly increases organismal exposure to exogenous chemicals and pathogens [7]. High concentrations of mycotoxins damage intestinal mucosal barrier function by affecting mucin mRNA expression levels, formation, secretion, and monosaccharide composition, leading to altered intestinal function and intestinal inflammatory diseases. Given the critical protective role of intestinal mucins in the mucosal barrier, this review examines the effects of mycotoxins on intestinal mucin production and the underlying mechanisms.

1 Overview of Intestinal Mucins

The intestinal mucosal barrier is primarily composed of the intestinal mucus layer, intestinal epithelial cells, and symbiotic microbial communities. Dysfunction of the intestinal mucus layer leads to systemic physiological disorders, including impaired immune function, weight loss, and reduced feed conversion efficiency [8]. Mucins secreted by intestinal goblet cells are the main constituents of the intestinal mucus layer. These glycoproteins combine with water to form a mucus layer covering the epithelial surface, providing lubrication and protection against pathogenic bacterial adhesion and invasion [9-10]. Intestinal mucins are high-molecular-weight glycoproteins [11] composed of a peptide core and carbohydrate chains. The peptide core is rich in threonine, serine, and proline residues, with carbohydrate chains predominantly attached via O-glycosidic bonds to threonine and serine residues, accounting for 50–70% of the mucin molecular mass [12] [Figure 1: see original paper]. A defining characteristic of intestinal mucins is extensive glycosylation, which largely determines the degree of mucosal protection [13].

Intestinal mucins are classified into two main types: membrane-bound and secreted. Membrane-bound mucins (cell surface mucins) include MUC1, MUC3A, MUC3B, MUC4, MUC12, MUC17, among others. Secreted mucins primarily include gel-forming mucins MUC2, MUC5AC, MUC5B, and MUC6 [14-15]. Different mucin types exhibit distinct expression patterns. Among the 21 identified mucin genes, 15 are expressed in various regions of the gastrointestinal tract [16-17]. Secreted mucins are typically found throughout the digestive tract in normal human physiology, whereas membrane-bound mucins are highly expressed in intestinal epithelial cells. For example, MUC3 is mainly expressed in the small intestine [9,19], MUC12 primarily in the colon [20], and MUC17 predominantly in the small intestine with high expression in the duodenum but also present in the transverse colon [21]. Secreted mucins form gel-like physical barriers on respiratory and digestive epithelial surfaces and in parenchymal organ ducts, providing essential physical and chemical protection, trapping foreign substances on epithelial surfaces, and maintaining growth factor concentrations. Membrane-bound mucins are thought to create steric hindrance, protecting vulnerable epithelial cells from external assaults and participating in protective extracellular mucin gel formation [22]. Under normal conditions, MUC2 in the human colorectum forms a protective barrier on the luminal epithelial surface against damage from harmful substances such as mycotoxins [12,23]. Membrane-bound mucins primarily participate in cell signaling, adhesion, growth, and immune regulation [9]. However, previous studies have demonstrated that the membrane-bound mucin MUC1 is also an important component of the intestinal mucosal barrier, as its protein levels are upregulated during pathogenic bacterial infection to suppress inflammation [24-26].

2.1 Effects of Mycotoxins on Monosaccharide Composition of Intestinal Mucins

Mycotoxin exposure alters the monosaccharide composition of intestinal mucins, subsequently modifying oligosaccharide components and structures of mucin O-glycans, ultimately affecting mucus layer integrity and intestinal microbiota composition. Common monosaccharides in mucins include N-acetylgalactosamine (GalNAc), N-acetylglucosamine (GlcNAc), galactose (Gal), fucose (Fuc), N-acetylneuraminic acid (NeuAc, also known as sialic acid), with small amounts of mannose (MAN) also detected [27]. Alpha- and beta-linked GalNAc, GlcNAc, and Gal constitute the primary structural components of intestinal mucin O-glycans, with core structures further elongated and diversified by fucosylation and sialylation.

Antonissen et al. [10] demonstrated that compared to controls, broiler chickens fed diets contaminated with DON (4.6 mg/kg), FBs (FB1+FB2, 25.4 mg/kg), or a combination of DON (4.3 mg/kg) and FBs (22.9 mg/kg) showed significantly increased proportions of GalNAc in duodenal mucin monosaccharide side chains in the FBs or DON+FBs groups, while galactose proportions decreased significantly. All mycotoxin groups exhibited significantly increased proportions of N-acetylneuraminic acid, while mannose proportions decreased in the FBs group and fucose proportions declined in the DON group. These results indicate that mycotoxins DON and FBs affect the duodenal mucus layer in broiler chickens by altering mucin monosaccharide composition.

Applegate et al. [28] reported that feeding laying hens diets containing 0, 0.6, 1.2, or 2.5 mg/kg aflatoxin B1 (AFB1) for two weeks resulted in no significant changes in body weight, feed intake, egg production, goblet cell number or density, or crude mucin secretion. However, intestinal crypt depth increased linearly with AFB1 concentration, and sialic acid secretion increased significantly by 12% when AFB1 concentration rose from 0.6 to 1.2 mg/kg. These findings demonstrate that even low mycotoxin concentrations can alter intestinal morphology and mucin monosaccharide composition in laying hens, changes that may enhance intestinal defense against mycotoxins.

2.2 Effects of Mycotoxins on Intestinal Mucin Expression Levels

In vivo and in vitro studies in humans, piglets, and mice have shown that mycotoxins, even at low concentrations, can affect intestinal goblet cell numbers, mucin mRNA expression levels, and protein expression, thereby damaging the intestinal mucus layer and triggering inflammation.

Bracarense et al. [29] demonstrated that feeding piglets diets contaminated with low concentrations of DON (3 mg/kg) or a DON+FBs mixture (3 mg/kg + 6 mg/kg) for five weeks reduced goblet cell numbers in the jejunum and ileum, suggesting that mycotoxins affect mucin secretion by influencing goblet cell pop-

ulations. Wan et al. [30] found that a DON and ZEA toxin mixture significantly increased goblet cell numbers (goblet cell hyperplasia), with MUC2 mRNA expression levels approximately 100% and 118% higher than control and pair-fed groups, respectively. Studies on the effects of individual or combined mycotoxins (DON, ZEA, NIV, FB1) on intestinal epithelial cells at various ratios showed that mycotoxins significantly altered MUC5AC and MUC5B mRNA and protein expression levels, though protein level changes were similar and less pronounced than transcriptional changes [31]. This indicates that post-transcriptional or post-translational regulatory mechanisms are closely associated with mycotoxin effects on mucin synthesis and secretion.

Furthermore, Pinton et al. [32] reported that human goblet cells (HT29-16E) and porcine intestinal explants exposed to DON for 48 hours showed dose-dependent downregulation of MUC1, MUC2, and MUC3 mRNA and protein expression, with significant effects observed at 1 mol/L. These studies demonstrate that mycotoxins affect both mRNA and protein expression levels of intestinal mucins, thereby influencing the intestinal mucosal barrier. The seemingly contradictory phenomena of mycotoxin-induced goblet cell reduction versus hyperplasia, and mucin expression upregulation versus downregulation, likely reflect activation of different protective and damaging mechanisms within the intestinal mucosal barrier that require further investigation. The regulatory effects of mycotoxins on intestinal mucins are not absolutely up- or down-regulatory but may vary depending on mycotoxin type, dose, exposure duration, and experimental subjects.

2.3 Mechanisms of Mycotoxin Effects on Intestinal Mucins

Mycotoxins affect intestinal mucins through two primary pathways: (1) directly activating cellular signaling pathways to influence mucin expression, and (2) disrupting the mucus layer and tight junctions, allowing pathogen invasion that directly activates signaling pathways or indirectly affects cytokine levels, thereby altering mucin expression [Figure 2: see original paper]. Research indicates that mitogen-activated protein kinase (MAPK), protein kinase R (PKR), c-Jun N-terminal kinase (JNK), nuclear factor- B (NF- B), and cytokines such as interleukin (IL)-1, IL-4, IL-6, IL-8, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ may mediate mycotoxin regulation of intestinal mucin expression.

Numerous studies have shown that DON activates multiple signaling pathways. Pinton et al. [32] investigated DON' s mechanism of action on intestinal mucins, demonstrating that DON primarily affects mucin mRNA and protein expression through PKR and MAPK p38 activation, ultimately inhibiting expression of resistin-like molecule β (RELMβ), a positive regulator of mucin expression. DON binding to ribosomes initially activates the PKR pathway, leading to MAPK p38 and ERK1/2 activation and ultimately inducing NF- B pathway activation [34-37]. NF- B activation is a common event in gastrointestinal inflammation, and MUC2 promoters containing NF- B binding sites have been identified. Nagashima [38] also implicated NF- B as an important factor in NIV

toxicity. These findings suggest that PKR, MAPK, and NF- B signaling pathways activated by mycotoxins are important regulators of intestinal mucins, with the NF- B pathway particularly implicated in mycotoxin regulation of MUC2 expression.

Additionally, mycotoxins indirectly affect mucin expression by influencing cytokine secretion. Wan et al. [39] demonstrated that four individual or combined Fusarium mycotoxins (DON, NIV, ZEA, FB1) at cytotoxic concentrations upregulated mRNA expression of pro-inflammatory cytokines IL-1α, IL-1β, IL-6, IL-8, and TNF-α in swine jejunal epithelial cells (IPEC-J2). DON regulates IL-1 and IL-8 expression in intestinal epithelial cells through PKR, p38, and NF- B pathways [40], while cytokines themselves regulate mucin expression. For example, Ahn et al. [41] showed that TNF-α activates NF- B to upregulate MUC2 transcription while simultaneously inhibiting MUC2 transcription through JNK activation. MUC3 expression is regulated by IL-4, IL-6, TNF-α, and IFN-γ, while IL-4, IL-9, TNF-α, and IFN-γ promote MUC4 expression [41-43]. These findings suggest that signaling pathways may mediate the entire process by which mycotoxins affect cytokines and subsequently regulate intestinal mucin expression.

Beyond these factors, leptin represents another important element potentially involved in mycotoxin regulation of mucin secretion. Leptin is a hormone released by the stomach and locally during inflammation that significantly influences mucin genes and belongs to the IL-6 family. Otero et al. [44] investigated leptin' s effects in both in vivo (rat colonic infusion model) and in vitro models (rat mucosal cells DHE and human goblet cells HT29-MTX), finding that leptin significantly stimulated mucin expression, though mucin secretion and expression were independent of endogenous leptin secretion. In rat mucosal DHE cells, leptin dose-dependently (0.01–10.00 nmol/L, 60 min) increased MUC2, MUC3, and MUC4 mRNA expression. In the rat colonic infusion model, leptin similarly upregulated MUC2, MUC3, and MUC4 mRNA expression. In human goblet cells HT29-MTX, leptin dose-dependently increased MUC2, MUC5AC, and MUC4 mRNA expression. Leptin binding to its receptor (Ob-R) may trigger multiple signaling pathways, including Janus kinase (JAK)/signal transducer and activator of transcription (STAT), MAPK, phosphatidylinositol 3-kinase (PI3K), and protein kinase C (PKC) pathways. However, leptin increases mucin expression primarily through PKC, PI3K, and MAPK pathways rather than JAK/STAT [45]. Additionally, Feng [46] demonstrated that ducks fed naturally moldy corn diets (exceeding AFB1 standards) exhibited increased mortality, reduced feed intake and weight gain, and improved feed nutrient digestibility. Further analysis revealed that reduced weight gain was primarily caused by decreased feed intake, with the mechanism involving increased serum leptin and decreased neuropeptide Y (NPY), suggesting that ducks may alleviate mycotoxin damage by increasing serum leptin and decreasing neuropeptide Y. Collectively, these findings indicate that leptin may play an important role in colonic mucosal barrier defense against toxins, potentially participating in mucin modulation to protect the intestinal mucosal barrier from mycotoxin exposure.

3 Summary

Exposure of the intestine to high concentrations of mycotoxins causes mucosal damage, leading to intestinal inflammation and cancer. Intestinal mucins, as primary components of the intestinal mucosal barrier, are critically important in the pathogenic mechanisms of mycotoxin-induced intestinal inflammation and cancer. Mycotoxin invasion triggers goblet cell changes (including hyperplasia), dysregulated mucin secretion, and alterations in mucin O-glycan structures. Changes in mucin O-glycan structures are closely associated with intestinal inflammation and cancer progression, as defective O-glycosylation substantially increases spontaneous colitis incidence. Moreover, intestinal mucins are intimately linked to tumor development, progression, and prognosis in other organs. However, current research on mycotoxin mechanisms of intestinal mucosal barrier damage, particularly regarding mucin regulation, remains limited. Future studies should integrate mycotoxins, cell signaling pathways, cytokines, and intestinal mucins to further elucidate the mechanisms of mycotoxin effects on the intestinal mucosal barrier. Such research would provide theoretical foundations for reducing and repairing mycotoxin-induced intestinal damage, thereby decreasing the incidence of animal intestinal inflammation, cancer, and related diseases in production systems while maximizing food safety for human consumption.

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