




Impact of mycotoxins on the intestine: are mucus and microbiota new targets?

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ABSTRACT

There is an increasing awareness of the deleterious effects attributed to mycotoxins during their fate within the gut, particularly for deoxynivalenol (DON), zearalenone (ZEN), ochratoxin A (OTA), fumonisin B1 (FB1), aflatoxin B1 (AFB1), and patulin (PAT). Evidence indicates that disruption of the epithelial barrier is well established. However, intestinal barrier function on its luminal side involves two other partners, mucus and microbiota, which have rarely been considered in the context of mycotoxin exposure. The current review aimed at providing a summary of DON, ZEN, OTA, FB1, AFB1, and PAT effects on intestinal barrier function, with special focus on mucus and microbiota. DON, ZEN, OTA, FB1, AFB1, and PAT are known to markedly affect epithelial cell integrity and functions. Regarding mucus, DON is the most documented mycotoxin. In vivo, toxicological impact of DON generally has only been assessed through goblet cell number. Evaluation of the mycotoxins/mucus interplay considering other indicators such as composition, thickness, and penetrability of mucus, mucin O-glycosylation thus warrants further attention. With respect to microbiota, few short-term studies to date have been reported indicating deleterious effects. However, long-term exposure to mycotoxins may also produce significant changes in microbiota composition and metabolic activity, which requires further experimentation. In conclusion, mucus and microbiota are key targets for dietary mycotoxins although assessment of induced effects is preliminary. A significant research effort is now underway to determine the adverse consequences of mycotoxins on mucus and microbiota considered as individual but also as tightly connected gut players.

Introduction

Mycotoxins are secondary metabolites produced by fungal genera mainly *Aspergillus*, *Fusarium*, and *Penicillium*. These metabolites represent the most frequently occurring natural food contaminants in human and animal diets and occur worldwide in foods such as cereals and animal forages (Bondy and Pestka 2000; Ok et al. 2009), leading to acute and chronic exposures in humans and animals (Akbari et al. 2017). Despite the improvement of good agricultural and manufacturing practices, mycotoxin contamination especially occupational cannot be avoided (Viegas et al. 2012, 2013; Follmann et al. 2016; Pinto et al. 2015) and recent surveys indicate that 70% of the raw materials are contaminated with these toxins (Bryden 2012; Streit et al. 2013). Mycotoxins are (1) produced before,

during and after harvest; (2) variably resistant to technological treatments and (3) sometimes difficult to eliminate. These metabolites are known to be present in human food and animal feed. The aim of this review is to focus on major mycotoxins: deoxynivalenol (DON), zearalenone (ZEN), ochratoxin A (OTA), fumonisin B1 (FB1), aflatoxin B1 (AFB1), and patulin (PAT). Generalities, regarding chemical structure, major producing fungi, predominant contaminated crops, adverse effects, mode of action, and health-based guidance values are presented in Table 1. As noted in this Table, the clinical toxicological syndromes initiated by chronic or sub-chronic ingestion of mycotoxins on animal health have been described leading to regulations for human food in many countries including USA and Europe.

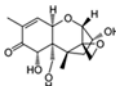
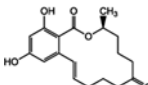
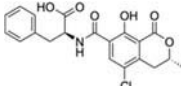
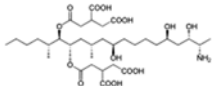
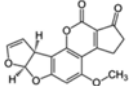
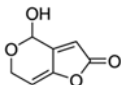
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Table 1. Major mycotoxins: formula, producing species, affected crops, adverse effects and health-based guidance values (adapted from Karlovsky et al. (2016)).

Mycotoxin	Chemical structure	Major producing fungi	Main contaminated crops	Main adverse effects & mode of action	Health-based guidance value
Deoxynivalenol (DON)		<i>Fusarium graminearum</i> , <i>F. culmorum</i>	Wheat, maize, barley, oats, rye	Feed refusal, emesis Reduction in growth Immunotoxicity Not classifiable as to carcinogenic to humans Binds to ribosomes and activates MAP Kinases	ARFD ^a 8 µg/kg bw/day TDI ^b 1 µg/kg bw/day group-PMTDI ^b (for DON and its acetylated forms) 1 µg/kg bw/day
Zearalenone (ZEN)		<i>F. graminearum</i> , <i>F. culmorum</i>	Wheat, maize, barley, oats, rye	Endocrine disruptor (interaction with estrogen-receptors)	PMTDI ^c 0.5 µg/kg bw/day TDI ^b 0.25 µg/kg bw/day
Ochratoxin A (OTA)		<i>Aspergillus</i> section <i>Circumdati</i> or section <i>Nigri</i> , <i>Penicillium verrucosum</i> , <i>P. nordicum</i>	Cereals, nuts, dried fruits, coffee, cocoa	Nephrotoxic (renal tumors) Carcinogenic to animals and possibly to humans	PTWI ^d 100–120 ng/kg bw/day
Fumonisin B1 (FB1)		<i>Fusarium</i> section <i>Liseola</i> , <i>Aspergillus niger</i>	Maize (<i>Fusarium</i> spp.) Grapes (<i>A. niger</i>)	Inhibition of sphingolipid biosynthesis Induction of apoptosis in liver Tumorigenic in rodents Possibly carcinogenic to humans	TDI ^b 2 µg/kg bw/day
Aflatoxin B1 (AFB1)		<i>Aspergillus</i> section <i>Flavi</i>	Maize, peanuts, nuts, pistachious, other dried fruits	Genotoxic carcinogen Carcinogenic to humans	Because of carcinogenicity, exposure should be kept as low as reasonably achievable. No official health-based guidance value
Patulin (PAT)		<i>Byssoclhamys nivea</i> , <i>Penicillium expansum</i> , <i>Aspergillus</i> section <i>Clavati</i>	Fruits especially apples, silage	Gastrointestinal ulceration Immunotoxicity Neurotoxicity	PMTDI ^c 0.4 µg/kg bw/day

^a: ARFD: Acute Reference Dose (for 1-day exposure) ^b: TDI: Tolerable Daily Intake ^c: PMTDI: Provisional Maximum Tolerable Daily Intake ^d: PTWI: Provisional Tolerable Weekly Intake

Numerous investigators demonstrated the adverse effects resulting from exposure to several mycotoxins on various indicators of growth performance. Indeed, both animal experiments and human epidemiological studies reported an impaired growth upon exposure to aflatoxins, fumonisins, or DON (Andretta et al. 2011, 2012; Khlangwiset, Shephard, and Wu 2011; Smith et al. 2015; Wu, Groopman, and Pestka 2014). The intestine may play a role in growth retardation induced by mycotoxins; however, except for DON, the underlying mechanism remains unknown. From studies mainly conducted in mice, Pestka and his colleagues demonstrated that DON acts at different levels to induce impaired growth and weight gain, including altered neuroendocrine signaling, immune responses, growth hormone disturbances, and

central nervous system changes (Lebrun et al. 2015; Wu, Groopman, and Pestka 2014, 2017; Zhou and Pestka 2015).

There is an increasing awareness of the deleterious effects of mycotoxins during their fate within the gastrointestinal tract (GIT). Mycotoxins induce intestinal pathologies in humans and animals, including necrosis of intestinal epithelium (Pinton and Oswald 2014), disturb intestinal barrier function, modulate immune responses, and indirectly affect feed consumption by impairing growth hormone signaling (Payros et al. 2016). Some mycotoxins induce DNA modifications and mutations in enterocytes (Maresca and Fantini 2010). Due to the diversity in their bioavailability, differences between animal species and enterohepatic recycling, mycotoxins may compromise intestinal homeostasis before absorption in the

upper compartments and/or throughout the entire intestine by a non-adsorbed or reabsorbed fraction (Grenier and Applegate 2013). These characteristics indicate that the GIT may repeatedly be exposed to a high proportion of ingested mycotoxins in its upper and lower segments. Indeed, the primary function of the GIT is digestion accompanied by water and nutrient absorption from the lumen to blood through the single-layered epithelium, which acts a selective filter against luminal pathogens and dietary antigens (Turner 2009). In addition, the ability of intestinal epithelial cells to act as immune cells and crosstalk with mucosal immunity (Gourbeyre et al. 2015; Shao, Kamalu, and Mayer 2005; Wells et al. 2011) will not be discussed in this review.

Numerous studies demonstrated mycotoxin-mediated disruption of the intestinal barrier integrity through an impairment of the epithelium barrier, as evidenced by increased permeability and translocation of harmful stressors such as pathogens (Akbari et al. 2017; Ghareeb et al. 2015; Grenier and Applegate 2013; Pinton and Oswald 2014). However, intestinal barrier function on its luminal side also involves two other partners, mucus and microbiota, which, together with epithelium, provide a physical, chemical, and biological line of defense for the host, probably in an orchestrated manner (Burger-Van Paassen et al. 2009; Da Silva et al. 2014; Lu et al. 2011; Tomas et al. 2013; Wrzosek et al. 2013). Although mucus and microbiota are key players in digestive health, these components have been frequently neglected in food toxicology and rarely considered in the context of mycotoxins. Based upon this background, the current review aimed to provide a summary of available evidence regarding direct effects of individual mycotoxins introduced above on intestinal barrier function, with special focus on mucus and microbiota.

The constituents of the intestinal barrier

Intestinal epithelium

The intestinal epithelium is the largest of the body's mucosal surfaces, encompassing approximately 400 m² surface areas with a single layer of columnar cells, organized into crypts and villi and

surrounded by the glycocalyx. There are many similarities in the histologic structure of the mucosa in the small and large intestine. The most apparent difference is that the large intestine is devoid of villi, which are “finger-like” structures conferring an increase in small intestinal absorptive surface. One absorptive (enterocytes/colonocytes) and four main differentiated (goblet cells, Paneth cells, enteroendocrine cells and tuft cells) cell types have to date been described in the intestinal epithelium. The most abundant are the enterocytes/colonocytes, which enable nutrients and water to be transported along the small and large intestine respectively into the internal environment. In the secretory cell lineage, the largest number is represented by goblet cells characterized by mucin-granule containing distended theca. Their number increases from the proximal to distal intestine, constituting 4, 6, 12, and 16% in the duodenum, jejunum, ileum, and distal colon, respectively. Paneth cells specifically located in the small intestine provide antibacterial peptides and proteins. The other secretory cells types such as enteroendocrine and tuft cells are less abundant (1 and 0.4%, respectively) and distributed all along the epithelium. The intestinal epithelial surface is continually renewed by pluripotent intestinal epithelial stem cells that reside in the base of crypts, where proliferation, differentiation, and functional potential of epithelial cell progenitors are regulated by local stem cell microenvironment (Crosnier, Stamataki, and Lewis 2006; Van Der Flier and Clevers 2009).

Intestinal epithelial cells display two crucial albeit opposite functions. Intestinal epithelial cells regulate nutrients and water absorption while restricting access for luminal antigens to permeate internal organs. Thus, these cells constitute a selective—and dynamic—barrier, mediating transport of molecules through the transcellular pathway (across cells) and/or the paracellular pathway (between cells). The major functional elements involved in the separation between apical (luminal) and basolateral compartments are the tight junction (TJ) proteins, sealing the intercellular space between adherent epithelial cells. TJ surrounds the apical ends of the lateral membranes of epithelial cells and determines the selective paracellular permeability to solutes (Tsukita,

Furuse, and Itoh 2001). TJ is multiple protein complexes composed of transmembrane proteins and a wide spectrum of cytosolic proteins. Four integral transmembrane proteins, including occludin, claudins, junctional adhesion molecule (JAM), and tricellulin have been identified with the claudin family consisting of at least 24 members. The intracellular domains of these transmembrane proteins interact with cytosolic scaffold proteins, such as zonula occludens (ZO) proteins, which subsequently anchor transmembrane proteins to the perijunctional actomyosin ring (Suzuki 2013). TJ ensures three main functions to: (i) provide a barrier to adverse luminal agents, (ii) allow the permeation of ions, solutes, and water, and (iii) maintain cell polarity by blocking free diffusion of proteins and lipids between apical and basolateral domains of the plasma membrane (Turner 2009). The modification of TJ barrier function and paracellular permeability is dynamically regulated by various extracellular stimuli and closely associated with health and susceptibility to disease (Turner 2009). Experimentally, the integrity of intestinal epithelial layer integrity may be assessed by measuring transepithelial electrical resistance (TEER). In addition, the intestinal permeability might be more specifically determined using markers of different sizes to evaluate the paracellular pathway such as Lucifer yellow, fluorescein isothiocyanate FITC, FITC-dextran, or chromium-labeled ethylenediamine-tetraacetic acid ^{51}Cr -EDTA and/or the transcellular pathway with larger molecules $> 4\text{kDa}$, such as horseradish peroxidase.

Intestinal mucus

Mucus and mucins

Few investigations have focused on GIT mucus since this substance is transparent and may collapse upon any manipulation. Indeed, mucus is mostly water ($>95\%$) and shrinks to a thin structure when dehydrated. That is why mucus is not normally observed on formaldehyde-fixed tissue sections and is best preserved using Carnoy fixative based on dry methanol, dry chloroform and glacial acetic acid (Puchtler et al. 1970). Atuma et al. (2001) took a big step forward in showing that the mucus luminal surface was visualized in rats by allowing charcoal particles to sediment

down on top of the mucus. Following this procedure, a relatively thick mucus layer was observed along the whole intestine. This pioneer work then fuelled numerous studies in mucus science for unraveling why this intestinal component functions as a key interface and its necessity for maintaining gut health in humans and animals. Mucus is a viscoelastic gel that lines and protects the intestinal epithelium, separating it from the contents of the lumen. Mucus functions as a dynamic barrier that is permeable to gases, water, and nutrients, but impermeable to most microorganisms. This substance was long considered to act as a “simple” physical barrier but is now known to exert other key functions essential for maintaining intestinal homeostasis, such as (i) lubrication of the epithelium, facilitating the progress of material along the digestive tract; (ii) maintenance of a stable microenvironment at the epithelial surface; (iii) protection of the epithelium through the presence of immune system molecules; and (iv) provision of an ecological niche for the intestinal microbiota (Johansson, Larsson, and Hansson 2011; Juge 2012; Ouwerkerk, De Vos, and Belzer 2013).

The main constituents of mucus are mucins, which are produced, stored, and released by goblet cells. Mucins are large glycoproteins in which the glycans make up more than 80% of the molecular mass. The central parts have a protein backbone containing sequences rich in proline, threonine, and serine, the so-called PTS-sequences, which are highly O-glycosylated and constitute mucin domains. The O-linked glycan chains contain 1–20 sugar residues, which might be attached in a linear and branched manner. The O-glycans are initially attached to a serine or a threonine of the protein backbone with N-acetylgalactosamine (GalNac). The chain is elongated with core structures and two potential backbone regions containing N-acetylglucosamine (GlcNac) and galactose (Gal). Termination usually occurs with fucose (Fuc), Gal, GalNac, or sialic acid residues that form the different histo-blood-group antigens. Both Gal and GlcNac residues may be sulfated, thus offering a high degree of diversification (Linden et al. 2008). MUC2 is the secreted gel-forming mucin present in the intestine (Johansson, Larsson, and Hansson 2011). MUC2 oligomerizes into large net-like polymers when the C- and N-termini form

disulfide bond-stabilized di- and trimers (Ambort et al. 2012). In humans, MUC2 is coated with more than 100 different O-linked glycan structures (Larsson et al. 2009), which notably differ from those in rodents (Thomsson et al. 2012). The difference in the glycan “preferences” of bacterial species was suggested to explain host-specific selection of a characteristic microbiome profile (Donaldson, Lee, and Mazmanian 2015).

Mucus in the small intestine and colon

Mucus covers the intestinal epithelium to a different extent along the GIT in humans and animals. The stomach and colon have a two-layered system with an inner and an outer mucus layers, whereas the small intestine has only a single layer (Ermund et al. 2013). In this region, the mucus fills up the space between the villi and covers them, but is not attached to the epithelium and is penetrable to particles with the same size as bacteria (Ermund et al. 2013). As mucus is not anchored to the epithelial surface, this substance moves with peristaltic waves in a distal direction. Fresh mucus is continuously secreted from the goblet cells, especially from the crypt openings.

In contrast to the small intestine, the colon exhibits a two-layered mucus system organization. The inner mucus layer is continuously formed by secretion from the surface goblet cells (Johansson 2012). Upon secretion, the MUC2 mucin unfolds and forms large net-like structures that are arranged by interacting with previously secreted inner mucus layer (Ambort et al. 2012). The inner mucus layer is firmly attached to the epithelium with a thickness of 50 μm and 200–300 μm in mice and humans, respectively (Atuma et al. 2001; Hansson and Johansson 2010; Johansson et al. 2008). An estimate of the turnover of the inner mucus layer in live murine distal colonic tissue suggests that it is renewed every 1–2 hr (Johansson 2012). This turnover kinetics is important for maintaining this layer free from bacteria (Johansson et al. 2008). Another important factor for the host protection is the staggered layers of MUC2 that act as a size-exclusion filter (Johansson et al. 2008; Round et al. 2012) and are thus not penetrable to bacteria or beads with sizes down to 0.5 μm (Johansson et al. 2014). The inner mucus layer is subsequently converted into the outer layer. This conversion, also observed in the mucus of

germ-free animals, probably depends upon host protease activities (Johansson et al. 2008). However, the nature of the protease(s) involved, and the activation trigger(s) remain to date unknown.

Intestinal microbiota

Gut microbiota of monogastric mammals contains members of the three domains of life (Archaea, Bacteria and Eukarya). Results presented here only focus on the bacterial microbiota composition and functions.

Composition and functions of the gut microbiota

Adult mammalian intestinal microbiota are dominated by two phyla, *Bacteroidetes* and *Firmicutes*, whereas *Actinobacteria* (including *Bifidobacterium* spp.), *Proteobacteria* (including *Escherichia coli* and *Enterobacteriaceae* family), and *Verrucomicrobia* (including *Akkermansia muciniphila*) phyla are only present in minor proportions (Bäckhed et al. 2005; Eckburg et al. 2005; Ley et al. 2008). Along the GIT, microbiota are not homogeneous and displays both longitudinal from stomach to distal colon (Donaldson, Lee, and Mazmanian 2015; Gu et al. 2013) and latitudinal from crypts to lumen heterogeneities (Nava, Friedrichsen, and Stappenbeck 2011; Pédrón et al. 2012). Although the microbiota composition under healthy conditions is relatively stable at the phylum level among individuals, a high variable bacterial composition at the species level was detected. However, the functional composition including metabolism of indigestible carbohydrates, proteins, and bile acids remains relatively stable (Rajilić-Stojanović et al. 2012; Shafquat et al. 2014). Some external host factors, such as diet (Davenport et al. 2014; Salonen and De Vos 2014), stressor exposure (Bailey et al. 2010), and antibiotic treatment (Maurice, Haiser, and Turnbaugh 2013), are known to exert a marked influence on bacterial gut microbiota. These changes may be transient for moderate or non-permanent perturbations as gut microbiota is considered to be relatively resilient (Lozupone et al. 2012).

The concentration and microbial diversity of gut microbiota increase from duodenum to distal colon segments. In fact, in humans, the bacterial concentration commonly rises by approximately 8 Log_{10} orders of magnitude from the beginning of small intestine (10^{3-4} CFU/g) to distal colon (10^{11-12} CFU/g) (Sekirov

et al. 2010). For healthy subjects, such high variations depend upon local gut physical parameters including pH, redox potential, oxygen concentration (Albenberg et al. 2014), and/or the presence of antimicrobial molecules (α - and β -defensins, lysozyme, RegIIIy), bile salts, reactive oxygen species (ROS), and digestive enzymes secreted by the host in the lumen.

Small intestine microbiota

The bacterial population inhabiting the small intestine possesses common traits to cope with a harsh physico-chemical environment, characterized by (1) high concentration of secreted bile acids, (2) rapid luminal flow, and (3) the presence of a small amount of oxygen. In humans, small intestine microbiota consists of facultative anaerobes (*Lactobacillaceae*, *Streptococcaceae*, *Enterobacteriaceae*) and strict anaerobes (*Veillonella* spp. and *Clostridium* cluster XIVa), belonging to *Proteobacteria* and *Firmicutes* phyla.

Large intestine microbiota

In the large intestine, non-digestible carbohydrates such as cellulose, hemicellulose, and resistant starch as well as host mucins are hydrolyzed. Degradation of polysaccharides including cellulose or hemicellulose, is performed by members of *Ruminococcus* and *Roseburia* genera belonging to the *Lachnospiraceae* family (*Clostridium* cluster XIVa) and *Firmicutes* phylum. Some members of *Prevotella* and *Bacteroides* genera (*Bacteroidetes* phylum) are also active in this degradation process (Louis, Hold, and Flint 2014; Rajilić-Stojanović 2013). Fermentation of monosaccharides then leads to the production of short chain fatty acids, in particular acetate, propionate, and butyrate. The latter is the primary energy source for colonocytes. This substance plays a key role in colon epithelial protection, against colorectal cancer by inhibiting HDACs (histone deacetylases) in cancerous cells and activating HATs (histone acetyltransferases) in normal cells. Further, butyrate makes immune system hyporesponsive to beneficial commensals (Donohoe et al. 2011; Hamer et al. 2008; Koh et al. 2016). The main butyrate producers identified to date belong to the *Lachnospiraceae* or the *Ruminococcaceae* family, notably *Faecalibacterium prausnitzii* (Louis et al. 2010), which also displays anti-inflammatory properties (Sokol et al. 2008).

Non-digested proteins or amino acids may be fermented by some proteolytic bacteria predominantly *Bacteroides* spp. However, some end-products of protein fermentation, such as p-cresol or hydrogen sulfide (H_2S), are considered as toxic metabolites for the host. Further, bile acids that escape from absorption in terminal ileum are deconjugated to a less toxic form by members of *Bacteroides*, *Lactobacillus*, and *Bifidobacterium* genera.

Gut microbiota determination is generally based on fecal material, but in recent years, increasing attention has been paid to bacteria living in close proximity to mucus, mucosa and/or crypts, and depicted as spatially organized biofilms at the mucosal surface (De Vos 2015; Nava, Friedrichsen, and Stappenbeck 2011; Pédrón et al. 2012).

Impact of mycotoxins on the gut: focus on epithelium, mucus, and microbiota

Data dealing with the impact of major mycotoxins, DON, ZEN, OTA, FB1, AFB1, and PAT on intestinal epithelium, mucus, and microbiota are summarized below.

Deoxynivalenol (DON)

Among the mycotoxins produced by the *Fusarium* genus, the broad family of trichothecenes is prevalent; in particular, deoxynivalenol (DON) is present in cereal-based products (Table 1). DON is toxic to humans and many animal species, with pig being the most sensitive species to this mycotoxin and chicken the most resistant one (Pestka and Smolinski 2005; Pinton and Oswald 2014). Ingestion of DON typically results in a variety of adverse symptoms in animals, such as irritation or necrosis of intestinal mucosa, diarrhea, vomiting, reduction in feed intake, low body weight gain, and alteration in immunological functions (Bondy and Pestka 2000; Maresca 2013; Pestka 2010; Wang et al. 2014). In humans, food poisoning with nausea, diarrhea, and vomiting was associated with *Fusarium*-infested or DON contaminated cereals. For example, in a gastroenteritis outbreak in the Anhui province of China affecting more than 130,000 people, wheat samples collected were found to contain 2 to 50 mg DON/kg food (Wu, Groopman, and Pestka 2014). At the molecular level, DON binds to the 60S ribosomal subunit, induces a

ribotoxic stress leading to the activation of MAP Kinases, cellular cell cycle arrest and apoptosis (Payros et al. 2016; Pestka 2010).

DON and intestinal epithelium

DON was shown to induce intestinal lesions in the jejunum and ileum in pigs, further confirmed in *ex vivo* studies using piglet jejunal explants (Lucioli et al. 2013; Pierron et al. 2016a; Pinton et al. 2012). In particular, shortening of villi height was found suggesting an effect of DON in the balance between epithelial cell proliferation and apoptosis. In rodents, sub-chronic exposure to DON-contaminated diet induced significant jejunal lesions associated with a lower height of villi (Payros et al. 2017). Such changes, also observed in broilers, led to an altered absorption by intestinal epithelial cells, thus adversely impacting animal growth (Ghareeb et al. 2015). In pigs with a low-dose exposure and treatment duration between 1 and 6 weeks, no significant differences in morphometric parameters characterizing the architecture of the mucosa that is thickness of the mucosa, height of the villi, and villus-to-crypt length ratio were noted in the duodenum of DON-exposed versus control animals (Lewczuk et al. 2016).

Regarding the effect of DON on the intestinal epithelial barrier, DON was found to affect TEER in porcine and human cells lines (Ghareeb et al. 2015; Pierron et al. 2016a; Pinton and Oswald 2014). Kasuga et al. (1998) reported that DON reduced TEER and increased permeability of Lucifer yellow in human Caco-2 and T84 cells. Similarly, DON enhanced paracellular permeability of porcine IPEC-1 cells and human Caco-2 cells to FITC-dextran in a time and concentration-dependent manner (Pinton et al. 2009). In piglet jejunal explants, a 2-fold elevation in paracellular passage of FITC-dextran was observed in comparison with untreated jejunal tissue (Pinton et al. 2009). *In vivo*, a reduction in TEER was associated with an increase in paracellular passage of FITC-dextran in the intestine of chickens, pigs, and mice exposed to DON (Akbari et al. 2014; Ghareeb et al. 2015; Pinton and Oswald 2014). In porcine epithelial cell monolayers, the rise in intestinal permeability was related to a specific reduction in expression of TJ proteins and more specifically claudins (Akbari et al. 2014; Diesing et al. 2011;

Pinton and Oswald 2014). In particular, diminished expression of claudin 4 was shown to be mediated by activation of the MAP kinase pathway (Lucioli et al. 2013; Pinton et al. 2010). The fall in protein expression was accompanied by an up-regulation, at least to some extent, of the TJ mRNAs levels both *in vitro* and *in vivo* (Akbari et al. 2014; Osselaere et al. 2013). Further, through activation of the MAP kinase pathway, DON induced a direct pro-inflammatory response increasing production of cytokines or chemokines, such as IL8, by intestinal epithelial cells (Alassane-Kpembé et al. 2017b; Cano et al. 2013; Maresca et al. 2008; Pierron et al. 2016a). Recently, Payros et al. (2017) demonstrated for the first time the implication of DON in DNA alteration of intestinal tissue. A significant rise in DNA damage was observed both *in vitro* and *in vivo* in intestinal epithelial cells of rodents colonized since birth by a commensal *E. coli* strain producing a genotoxin, the colibactin, and co-exposed to DON, compared to animals colonized only with *E. coli* strain and fed a control diet.

Alterations in the intestinal epithelium integrity are subsequently responsible for the entry of commensal and/or pathogenic bacteria, which normally are restricted to the gut lumen. Pinton et al. (2009) found that DON induced a concentration-dependent translocation of a pathogenic strain of *E. coli* across porcine IPEC-1 cells. Similarly, a significant elevation in passage of *Salmonella typhimurium* was observed in porcine IPEC-J2 cells after DON exposure (Vandenbroucke et al. 2011). In human DON-exposed Caco-2 cells, Maresca et al. (2008) confirmed the facilitated transepithelial passage of noninvasive commensal *E. coli*. In mice, ingestion of DON-contaminated feed potentiated *Salmonella enteritidis* infection (Hara-Kudo et al. 1996).

DON and intestinal mucus

Based upon *in vivo* experiments, results suggest that DON may compromise mucus barrier integrity. In piglets fed DON-contaminated feed for 5 weeks, Bracarense et al. (2012) reported a decrease in number of goblet cells in the jejunum, in comparison with controls. In a study on piglet jejunal explants exposed to DON, Basso, Gomes, and Bracarense (2013) noted the deleterious effect exerted by this

mycotoxin on goblet cells. However, in pigs fed DON-contaminated feed for 1–6 weeks, the % goblet cells in the epithelium covering the villi and forming the crypts were similar in duodenum of treated and control animals (Lewczuk et al. 2016). Interestingly, Pinton et al. (2015) used an *in vitro* human mucosecreting cell line (HT29-16E), as well as porcine jejunal explants, to determine the influence of DON on intestinal mucus. Sub-toxic doses of DON were found to reduce intestinal mucin production through a specific decrease in levels of mRNA encoding for the membrane-associated mucin MUC1 and the secreted mucins MUC2 and MUC3. Wan et al. (2014) also examined the DON-induced impact on mucus by considering human mucosecreting HT29-MTX cells alone or in co-culture with Caco-2 cells. *MUC5AC* and *MUC5B* mRNA and protein and total mucin-like glycoprotein secretion were significantly modulated. In particular, in the HT29-MTX monoculture, a significant downregulation of *MUC5AC* mRNA level was observed. In the Caco-2/HT29-MTX (70/30) co-culture, a significant downregulation of *MUC5AC* mRNA expression was found, while the *MUC5B* mRNA level was upregulated. When the HT29-MTX monoculture was used, a significant increase in the *MUC5AC* and *MUC5B* protein levels was noted in cell lysate. In the 90/10 co-culture, a significant increase in the *MUC5B* protein supernatant level was observed. In the 70/30 co-culture, a fall in *MUC5AC* protein levels was also found in cell supernatant. Finally, when the HT29-MTX monoculture was examined, DON significantly elevated total mucin in cell lysate, whereas, in the 70/30 co-culture, it significantly decreased the total mucin level in cell lysate and in cell supernatant. To date, the only *in vivo* apparent study reported on the properties of the mucus layer, referred here as an “extrinsic component” of the intestinal barrier, has been conducted in broiler chickens fed a DON-contaminated diet for 2 weeks (Antonissen et al. 2015). In the mycotoxin-exposed group, mRNA expression levels of *MUC2* were diminished in duodenum but not jejunum and ileum. Significant differences were observed in mucin monosaccharide composition between control and mycotoxin-challenged animals as evidenced by increase in GalNac and NeuAc proportions and reduction in Gal proportion in the duodenum (Antonissen et al. 2015). Antonissen et al. (2015)

suggested that such changes in mucin O-linked oligosaccharide composition might affect the mucus layer integrity (Da Silva et al. 2014) and modulate intestinal microbiota composition, even though no experimental evidence was provided.

DON and intestinal microbiota

One of the first studies in pigs examined the possible interaction between DON and gut microbiota based upon the use of the Capillary Electrophoresis-Single Strand Conformation Polymorphism (CE-SSCP) method to determine an effect on microbial populations through increase in total number of cultivable aerobic bacteria in feces (Waché et al. 2009). Further, after a 4-week DON administration in human microbiota-associated rats which are gnotobiotic rats harboring human intestinal microbiota, Saint-Cyr et al. (2013) employed a qPCR approach to demonstrate a significant elevation of 0.5 log₁₀ in the *Bacteroides/Prevotella* group and a decrease in *E. coli* in the fecal population. Recently, a 16S rRNA microbiota analysis showed that ingestion of a DON-contaminated diet in rodents did not significantly alter composition and diversity of gut microbiota (Payros et al. 2017).

It appears that DON may or may not exert a global effect on microbiota composition. Reciprocally, gut microbiota of various animals including rat, pig, cow, and chicken metabolizes DON (Hedman and Pettersson 1997; Payros et al. 2016; Swanson et al. 1987). Young et al. (2007) demonstrated de-epoxidation of DON to DOM-1 (deepoxy-deoxynivalenol), a less toxic metabolite by chicken intestinal microbiota (Pierron et al. 2016b). Interestingly, a member of the *Eubacterium* genus, the strain BBSH 797 isolated from bovine rumen fluid, is also able to de-epoxidize DON and used commercially (Fuchs et al. 2002; He and Zhou 2010). Similarly, in humans, the capacity of fecal microbiota to metabolize DON to DOM-1 was noted by Gratz, Duncan, and Richardson (2013) albeit this process is variable among individuals depending upon microbiota composition. A summary of the effects of DON on intestinal epithelium, mucus, and microbiota is provided in Table 2.

Zearalenone (ZEN)

Zearalenone (ZEN), which is produced by *Fusarium* species, is a natural contaminant of the food chain in countries with temperate

Table 2. Effects of deoxynivalenol on intestinal epithelium, mucus and microbiota.

Intestinal partner	Experimental model	Conditions	Effects	References			
Epithelium	Human and piglet cells	Various doses and durations	Decrease in cell survival	Increase in cell apoptosis	(Pinton and Oswald 2014)		
			Decrease in TEER and increase in permeability	Increase in bacterial translocation	(Ghareeb et al. 2015)		
	Rat IEC-6 cells	0–50 µM 4–8 h	Increase in DNA damage	Increase in lesional scores	(Akbari et al. 2017)		
			Decrease in TEER and increase in permeability	Increase in bacterial translocation	(Payros et al. 2016)		
	Piglet jejunal explants	Various doses and durations	Decrease in expression of TJ proteins	Increase in lesional scores	(Payros et al. 2017)		
			Increase in cell apoptosis	Increase in lesional scores	(Pinton and Oswald 2014)		
	Piglet, chicken, rodent	Various administration modes (contaminated diet, oral gavage), doses and durations	Decrease in TEER and increase in permeability	Increase in bacterial translocation	(Ghareeb et al. 2015)		
			Increase in cell apoptosis	Increase in bacterial translocation	(Akbari et al. 2017)		
	Pig	Water-soluble capsules	No change in the thickness of the mucosa, the height of the villi and the villus-to-crypt length ratio in the duodenum		(Payros et al. 2016)		
					(Lewczuk et al. 2016)		
Rat	12 µg/kg bw/day 1–6 weeks	Contaminated diet	Increase in jejunal lesions	(Payros et al. 2017)			
		10 mg/kg feed 4 weeks	Decrease in villi height				
Rat	Contaminated diet	2–10 mg/kg feed 1–4 weeks	Increase in DNA damage at adulthood	(Payros et al. 2017)			
Mucus	Human HT29-16E cells	0.1–100 µM 6–48 h	Decrease in mucin production	Decrease in <i>MUC1</i> , <i>MUC2</i> and <i>MUC3</i> mRNA	(Pinton et al. 2015)		
	Human HT29-MTX and/or Caco-2 cells	2 µM 48 h	Modulation of mRNA and protein of MUC5AC and MUC5B and mucin-like glycoprotein		(Wan et al. 2014)		
	Piglet jejunal explants	10 µM 4 h	Decrease in the number of goblet cells		(Basso, Gomes, and Bracarense 2013)		
	Pig	Contaminated diet 3 mg/kg feed 5 weeks	Water-soluble capsules	No change in the percentage of goblet cells in the epithelium covering the villi and forming the crypts in the duodenum		(Bracarense et al. 2012)	
					(Lewczuk et al. 2016)		
	Chicken	12 µg/kg bw/day 1–6 weeks	Contaminated diet	Decrease in mRNA expression of <i>MUC2</i> in the duodenum	Significant increase in monosaccharide composition (GalNac and NeuAc)	(Antonissen et al. 2015)	
Microbiota	Pig	4.6 mg/kg feed 2 weeks	Contaminated diet	Decrease in Gal proportion in the duodenum	Increase in cultivable total aerobic bacteria	Change in intestinal microflora (CE-SSCP profiles)	(Waché et al. 2009)
	Rat	2.8 mg/kg feed 4 weeks	Oral gavage	Increase in <i>Bacteroides/Prevotella</i> group	Decrease in <i>Escherichia coli</i>		(Saint-Cyr et al. 2013)
Rat	100 µg/kg bw/day 4 weeks	Contaminated diet	No change in the composition and the diversity of the gut microbiota			(Payros et al. 2017)	
		10 mg/kg feed 4 weeks					

climate (Bennett and Klich 2003; Richard 2007) (Table 1). Toxicity of ZEN on the reproductive tract is well characterized (Kowalska, Habrowska-Górczyńska, and Piastowska-Ciesielska 2016); ZEN possesses an estrogen-like activity competing with endogenous hormones for binding to the estrogen receptors

leading to hyper-estrogenism, precocious puberty, and reproductive disorders (Afriyie-Gyawu et al. 2005; Zhao et al. 2013).

ZEN and intestinal epithelium

ZEN decreased the survival of intestinal epithelial cells without altering TEER *in vitro*. This mycotoxin also

up-regulated expression of some genes implicated in cellular differentiation (*TFF2*, *BMP4*) and down-regulated the expression of tumor suppressor genes *DKK1*, *PCDH11X*, or *TC5313860* (Marin, Motiu, and Taranu 2015; Taranu et al. 2015; Wan, Turner, and El-Nezami 2013a). *In vivo*, in pigs fed ZEN-contaminated feed for 1–6 weeks, the thickness of the mucosa, height of villi, and villus-to-crypt length ratio were similar in duodenum of treated versus controls (Lewczuk et al. 2016).

ZEN and intestinal mucus

Few investigations to date examined the role of ZEN on intestinal mucus. The influence of ZEN on mucus was assessed *in vitro*, using HT29-MTX cells alone or in co-culture with Caco-2 cells (Wan et al. 2014). Recently, Lewczuk et al. (2016) reported that in pigs fed ZEN-contaminated feed for 1–6 weeks, the % goblet cells in duodenum remained unchanged.

ZEN and intestinal microbiota

Piotrowska et al. (2014) determined the cultivable bacterial populations, present in ascending colon of pigs fed ZEN-containing feed. The community structure, which includes diversity and richness, was estimated using the BIOLOG method. This method analyzes *in vitro* the consumption patterns of individual carbon substrates by the microbial communities. Data showed that ZEN reduced the levels of total cultivable aerobic bacteria. A summary of the effects of ZEN on intestinal epithelium, mucus, and microbiota is presented in Table 3.

Ochratoxin A (OTA)

Ochratoxin A (OTA) is produced by the fungi *Aspergillus* section *Flavi*, *Penicillium verrucosum*, and *Penicillium nordicum* (Table 1). This mycotoxin contaminates a wide variety of commodities and bio-accumulates in blood and milk of mammals exposed to OTA. In several animal species, OTA is a potent renal carcinogen by decreasing kidney function and inducing renal adenomas or carcinomas. The International Agency for Research on Cancer (IARC) thus considers OTA as possibly carcinogenic to humans (Group 2B) (Clark and Snedeker 2006; Kőszegi and Poór 2016; Pfohl-Leszkowicz and Manderville 2007).

OTA and intestinal epithelium

Although the kidney is the main target for OTA-induced toxicity, histological abnormalities and lesions of the GIT were reported. In particular, in chickens, a decrease in villi height was observed, in combination with an increase in necrosis and apoptosis of intestinal epithelial cells with prismatic epithelium and alterations of brush border (Solcan et al. 2015). Interestingly, a rise in crypt depth was also detected, as a compensatory process to shortening of villi.

Several *in vitro* studies showed that OTA inhibited cell growth, enhanced apoptosis, diminished TEER, and increased permeability to mannitol or FITC-dextran (Lambert et al. 2007; Maresca et al. 2001; Ranaldi et al. 2009). When human Caco-2 cells were exposed to OTA, translocation of commensal *E. coli* K12 strain was facilitated (Maresca et al. 2008). A reduction in expression of TJ proteins, namely claudins 3 and 4, was noted, and these adverse effects on intestinal permeability were associated with an elevation in OTA absorption and, thus, toxicity on systemic organs (Lambert et al. 2007; Maresca et al. 2001; McLaughlin et al. 2004).

Treatment of epithelial esophageal cells (Het-1A) with OTA induced DNA double strand breaks and chromosome aberrations with the observation of dicentric chromosome, ring chromosome, and chromosome breaks and gaps in a concentration-dependent manner (Liu et al. 2015). Further, these changes were associated to G2 cell cycle arrest and cellular apoptosis (Cui et al. 2010; Liu et al. 2015).

OTA and intestinal mucus

In an early study, Lee, Beery, and Chu (1984) investigated the localization of OTA in the gut of mice orally administered a single dose of mycotoxin. OTA was predominantly found to be present in the surface mucus of stomach. To the best of our knowledge, no other apparent data are available on this mycotoxin.

OTA and intestinal microbiota

Guo et al. (2014) investigated in rats the effects of a 28-day OTA administration on fecal microbiota composition. Bacterial composition was determined by 16S rRNA levels. In parallel, shotgun sequencing was performed to evaluate changes in functional genes. OTA treatment was shown to enhance relative abundance

Table 3. Effects of zearalenone on intestinal epithelium, mucus and microbiota.

Intestinal partner	Experimental model	Conditions	Effects	References
Epithelium	Porcine IPEC-1 cells	10–100 μ M	Decrease in survival rate	(Marin, Motiu, and Taranu 2015)
		10 μ M 24 h	No effect on cell viability	
	Porcine IPEC-J2 cells	0–40 μ M 48 h	Up-regulated expression of proliferative genes (<i>BMP4</i> , <i>CD67</i>) Down-regulated expression of tumor suppressor genes (<i>DKK-1</i> , <i>PCDH11X</i> , <i>TC5313860</i>) Decrease in survival rate	(Taranu et al. 2015)
	Pig	Water-soluble capsules 40 μ g/kg bw 1–6 weeks	No change in the thickness of the mucosa, the height of the villi and the villus-to-crypt length ratio in the duodenum	(Lewczuk et al. 2016)
Mucus	Human HT29-MTX and/or Caco-2 cells	40 μ M 48 h	Modulation of mRNA and protein of MUC5AC, MUC5B and mucin-like glycoprotein	(Wan et al. 2014)
	Pig	Water-soluble capsules 40 μ g/kg bw 1–6 weeks	No change in the percentage of goblet cells in the epithelium covering the villi and forming the crypts in the duodenum	(Lewczuk et al. 2016)
Microbiota	Pig	Oral gavage 40 μ g/kg bw/day 6 weeks	Reduction in total cultivable aerobic bacteria	(Piotrowska et al. 2014)

of members of the *Lactobacillaceae* family, accompanied by an elevation in facultative anaerobes and fall in microbial α -diversity. Guo et al. (2014) suggested that absorption, rather than hydrolysis, was the main route by which *Lactobacillus* species was able to detoxify OTA. Such modifications of gut bacteria composition, together with alterations in specific functional genes, including signal transduction, sugar, and amino acid transport systems clearly indicated that chronic exposure to OTA may be involved in shaping gut microbiota. A summary of the effects of OTA on intestinal epithelium, mucus, and microbiota is provided in Table 4.

Fumonisin B1 (FB1)

Fumonisin B1 (FB1) is produced by the fungi *F. verticillioides*, *F. proliferatum*, and some related species from the *Fusarium* section *Liseola* (Marasas 2001; Norred 1993) (Table 1). These mycotoxins mainly contaminate maize in the field. The family of fumonisins includes more than 22 congeners classified into four groups: A, B, C, and P. Among fumonisins, the most prevalent that contaminates feed and food is fumonisin B1 (FB1). FB1 toxicity was described in several animal species, including horses where it

induced encephalomalacia leading to death (Marasas 2001). Several studies demonstrated hepatotoxic, nephrotoxic, carcinogenic, immunotoxic, and reprotoxic effects attributed to FB1 (Norred 1993; Riley et al. 1994). In South Africa, a correlation was established between high human esophageal cancer rates and fumonisin-contaminated diet (Sun et al. 2007), and, since 2002, FB1 is considered by IARC as possibly carcinogenic to humans (Group 2B). At the molecular level, FB1 acts as a potent inhibitor of ceramide synthase, a key enzyme in the *de novo* synthesis, and turnover of complex sphingolipids, leading to decrease in concentration of sphingomyelin and glycosphingolipids, which participate to the composition of cellular membranes (Wang et al. 1991).

FB1 and intestinal epithelium

FB1 was found to (1) alter viability and proliferation of intestinal epithelial cells, (2) modulate the production of pro-inflammatory cytokines (IL8), and (3) affect the intestinal barrier function (Bouhet and Oswald 2007). In fact, in porcine IPEC-1 cells, FB1 decreased the survival rate in a concentration-dependent manner, which was also reported in human Caco-2 and HT29 cells (Kouadio et al. 2005; Minervini et al. 2014; Wan, Turner, and El-Nezami 2013a). Through the

Table 4. Effects of ochratoxin A on intestinal epithelium, mucus and microbiota.

Intestinal partner	Experimental model	Conditions	Effects	References
Epithelium	Human Caco-2 cells	100 μ M 24 h	Decrease in expression of claudins 3 and 4 Removal of claudins from microdomains to intracellular compartments	(Lambert et al. 2007)
		100 μ M 24 h	Increase in permeability to FITC-dextran	(McLaughlin et al. 2004)
		40 μ M— 1 mM 48 h	Increase in paracellular permeability to mannitol Intracellular redistribution of claudin 4 Increase in cell apoptosis	(Ranaldi et al. 2007)
		10 mM	Up-regulation of <i>MT2A</i> gene expression Increase in cell apoptosis	(Ranaldi et al. 2009)
	Human Caco-2 and HT29 cells	0–100 μ M 72 h	Decrease in TEER in a dose-dependent manner Decrease in cell growth	(Maresca et al. 2001)
		10 μ M 48 h	Potentialization of its own absorption by increasing paracellular permeability	
	Human Het 1-A cells	0–100 μ M 24 h	Induction of DNA strand breaks and chromosome aberrations G2 cell cycle arrest Down-regulation of Cdc2 and cyclin B1 protein expression Increase in apoptosis and activation of the cleavage of caspase 3	(Liu et al. 2015)
	Human GES-1 cells	0–100 μ M 24 h	G2 cell cycle arrest	(Cui et al. 2010)
		Long-term exposure	Induction of oxidative damage (ROS production) Increase in proliferation, migration and invasion Activation of Wnt/ β catenin pathway Induction of anchorage-independent growth of cells in soft agar	(Jia et al. 2016)
		40 weeks		
Chicken	Oral gavage	Decrease in body weight gain Decrease in small intestine villi height Small intestine crypt hypertrophy Induction of cells with multiple nuclei rich in dispersed chromatin	(Solcan et al. 2015)	
		1–50 μ g/kg bw/day 2 or 4 weeks		
Mucus	Mice	Oral gavage 25 mg/kg bw	Presence in the surface mucus of stomach	(Lee, Beery, and Chu 1984)
Microbiota	Rat	Oral gavage 70 and 210 μ g/kg bw 28 days	Enhancement of <i>Lactobacillaceae</i> family Increase in facultative anaerobes Decrease in microbial α -diversity	(Guo et al. 2014)

inhibition of the ceramide synthase and thus disruption of lipid metabolism as first molecular event, FB1 increased lipid peroxidation and free sphinganine levels in intestinal epithelial cells, inducing a block of cells in G0/G1 phase which resulted in cell growth inhibition and induction of apoptosis (Bouhet et al. 2004; Minervini et al. 2014). In piglets, exposure to FB1 elevated the ratio of sphinganine to sphingosine and altered distribution of glycoproteins in the jejunum (Loiseau et al. 2007). An increase in transepithelial passage of FB1 was also observed in IPEC-1 cells (Loiseau et al. 2007). In addition, FB1 was found *in vivo* and *ex vivo* to alter intestinal barrier integrity, diminishing the expression levels of TJ proteins (E-cadherin, occludin) while enhancing transcellular

permeability and bacterial translocation (Basso, Gomes, and Bracarense 2013; Bracarense et al. 2012; Lallès, Lessard, and Boudry 2009; Lessard et al. 2009).

FB1 and intestinal mucus

Brown, Rottinghaus, and Williams (1992) first reported that FB1 at high doses was responsible for intestinal goblet cell hyperplasia in intoxicated broiler chickens. Bracarense et al. (2012) in piglets fed fumonisin (FB1/FB2 mixture) noted a fall in number of goblet cells in the ileum, while in the jejunal segment, the number remained unchanged. In contrast, in a study on piglet jejunal explants exposed to FB1, Basso, Gomes, and Bracarense (2013) observed a reduction in number of goblet

cells. In broiler chickens fed a FB1/FB2 mixture-contaminated diet for 2 weeks, the mRNA expression level of *MUC2* was lowered in the duodenum, which was accompanied by significant differences in the mucin monosaccharide composition with a rise in GalNac and NeuAc proportions, and decrease in Gal proportion (Antonissen et al. 2015). To the best of our knowledge, the only study *in vitro*, demonstrating the impact of FB1 on mucus through *MUC5AC* and *MUC5B*, was reported by Wan et al. (2014) on HT29-MTX cells, alone or in combination with Caco-2 cells. In particular, Caco-2/HT29-MTX (90/10) co-culture incubation with FB1 significantly upregulated *MUC5AC* and *MUC5B* mRNA levels. In the 70/30 co-culture, significant downregulation of *MUC5AC* and *MUC5B* mRNA expression was noted. In the 90/10 co-culture, FB1 significantly increased the *MUC5AC* protein level in cell lysate but led to diminished levels in cell supernatant. Conversely, no marked changes in the *MUC5B* protein levels in cell lysate were observed. In the 70/30 co-culture, FB1 significantly decreased the total mucin level in cell lysate.

FB1 and intestinal microbiota

The only apparent study reported was in pigs by Burel et al. (2013) who observed a transient change in similarity between microbial CE-SSCP profiles after a fumonisin-based feeding. A summary of the influence of FB1 on intestinal epithelium, mucus, and microbiota is presented in Table 5.

Aflatoxin B1 (AFB1)

Aflatoxins, which are mainly produced by *Aspergillus flavus*, *A. parasiticus*, and some related species from *Aspergillus* section *Flavi*, represent a large family of mycotoxins present in a wide variety of cereals and tropical and sub-tropical food/feed stuffs (Table 1). The most abundant form of aflatoxins is aflatoxin B1 (AFB1), which exerts a potent genotoxic and carcinogenic effect in humans and animals. Indeed, AFB1 is the most potent hepatic carcinogen known in mammals and classified by IARC in Group I (carcinogenic to humans). AFB1 targets the liver and increases the development of hepatic cancers and acute aflatoxicosis. Aflatoxicosis is an acute hepatitis associated with vomiting, abdominal pain, and edema and may lead

to death. In 2004 in Kenya, an aflatoxicosis outbreak, associated with excessive aflatoxin concentrations in maize, resulted in 317 cases and 125 deaths (Azziz-Baumgartner et al. 2005). Among animal species, poultry is extremely sensitive to AFB1, resulting in decreased growth and egg production as well as increased susceptibility to diseases and other adverse effects including immunotoxicity (Jakhar and Sadana 2004).

AFB1 and intestinal epithelium

Few studies have to date reported the effect of AFB1 on intestinal epithelium. In human Caco-2 cells, AFB1 decreased TEER (Gratz et al. 2007), altered cell viability and growth, accompanied by increased lactate dehydrogenase (LDH) activity release and DNA damage (Zhang et al. 2015). Several *in vivo* studies in broilers noted that dietary exposure to AFB1 at low doses reduced the density of whole intestine (weight/length), suggesting a diminished absorptive area. However, at higher doses, no histological changes were observed (Kana et al. 2011; Ledoux et al. 1999; Yunus et al. 2011). The number of apoptotic cells in the jejunum and expression levels of *Bax* and *caspase-3* genes was elevated in chickens fed AFB1-contaminated diet in comparison with controls. This was associated with a lower jejunal villi height and less proliferation of cell nuclear antigen-positive cells (Peng et al. 2014; Zhang et al. 2014). In rodents, AFB1 induced intestinal lesions in the duodenum and ileum, characterized by a leucocytic and lymphocytic infiltration (Akinrinmade, Akinrinde, and Amid 2016).

AFB1 and intestinal microbiota

In a study conducted in rats following AFB1 chronic exposure, Wang et al. (2016), using 16S rRNA sequencing, observed a reduction in microbial diversity in the colon. An adverse effect on lactic acid bacteria population after treatment was noted, while the proportion of *Firmicutes* and *Bacteroidetes* remained unchanged. Using a cultural method, Galarza-Seeber et al. (2016) examined the total aerobic, facultative anaerobe (coliforms) and lactic acid bacterial populations in cecum of broilers exposed to AFB1. At the highest dose tested, the coliform population was 10-fold higher, whereas, for other microbial populations under study, only a numerical non-significant rise was observed. A summary of the influence of AFB1 on

Table 5. Effects of fumonisin B1 on intestinal epithelium, mucus and microbiota.

Intestinal partner	Experimental model	Conditions	Effects	References	
Epithelium	Porcine IPEC-1 cells	0–40 µM 48 h	Decrease in survival rate	(Wan, Turner, and El-Nezami 2013a)	
		> 100 µM 48 h > 20 µM 6 days	Increase in sphinganine concentration in a concentration-dependent manner	(Loiseau et al. 2007)	
		200 µM 16 days	Increase in transepithelial flux of FB1		
	Human HT29 cells	0–69 µM 12–72 h	2–700 µM 48 h	Decrease in survival rate of proliferative and differentiated cells G0/G1 cell cycle arrest	(Bouhet et al. 2004)
				Decrease in TEER in a concentration-dependent manner	
				Inhibition of cell proliferation	(Minervini et al. 2014)
	Human Caco-2 cells	1–150 µM 72 h		Increase in microviscosity of the cellular membrane	
				Increase in lipid peroxidation	
	Pig jejunal explants	100 µM 4 h		Decrease in cell viability	(Kouadio et al. 2005)
				Decrease in expression of E-cadherin	(Basso, Gomes, and Bracarense 2013)
	Pig	10 µM 2 h		Increase in TEER	(Lallès, Lessard, and Boudry 2009)
				Increase in permeability to horseradish peroxidase	
				Increase in production of stress proteins: COX-1, nNOS, hsp70 and HO-2	(Lallès et al. 2010)
		Bolus oral administration 1.5 mg/kg bw/day 9 days		Increase in ratio of sphinganine to sphingosine	(Loiseau et al. 2007)
				Changes in the distribution of glycoproteins in the jejunum	
Oral gavage 2.8 µmol/kg bw/day 2 weeks			Reduction in villi height	(Grenier et al. 2012)	
			Increase in lesional scores		
Contaminated diet 5.9 mg (4.1 mg FB1 + 1.8 mg FB2)/kg feed 5 weeks		Reduction in cell proliferation in the jejunum	(Bracarense et al. 2012)		
		Decrease in expression of E-cadherin and occludin			
		Reduction in villi height and induction of atrophy and fusion of villi			
Rodent	Contaminated diet 810 mg/kg bw/day 90 days		Increase in number of mitotic cells in the small intestine	(Theumer et al. 2002)	
			Increase in necrosis and immune cell infiltrate	(Casado et al. 2001)	
Human HT29-MTX and/or Caco-2 cells	40 µM 48 h		Modulation of mRNA and protein of MUC5AC, MUC5B and mucin-like glycoprotein	(Wan et al. 2014)	
			Reduction in the number of goblet cells	(Basso, Gomes, and Bracarense 2013)	
Pig jejunal explants	100 µM 4 h		Reduction in the number of goblet cells in the ileum	(Bracarense et al. 2012)	
Mucus	Chicken	Contaminated diet 300 mg/kg bw 2 weeks	Hyperplasia of goblet cells	(Brown, Rottinghaus, and Williams 1992)	
Contaminated diet 25.4 mg (FB1 +FB2)/kg feed 2 weeks		Decrease in mRNA expression of <i>MUC2</i> in the duodenum	(Antonissen et al. 2015)		
		Significant increase in monosaccharide composition (GalNac and NeuAc)			
Microbiota	Pig	Contaminated diet 11.8 mg/kg feed 9 weeks	Decrease in Gal proportion in the duodenum		
			Global effect on gut microbiota (CE-SSCP profiles)	(Burel et al. 2013)	

intestinal epithelium and microbiota is provided in Table 6. To the best of our knowledge, there are no apparent data available to date on intestinal mucus.

Patulin (PAT)

Patulin (PAT) is an unsaturated heterocyclic lactone, mainly produced by several fungal species belonging to *Penicillium*, *Aspergillus*, *Paecilomyces*, and *Byssoschlamys* (Table 1). Patulin is frequently detected in moldy fruits, fruit products, barley, wheat, corn, and their processed products. PAT was originally identified for its antibiotic properties, but mycotoxin-mediated neurotoxicity led to its abandonment as a therapeutic substance (Puel, Galtier, and Oswald 2010). This mycotoxin is highly reactive towards thiol groups of proteins and glutathione (GSH) and produces structural DNA damage (Glaser and Stopper

2012). Since 1986, PAT is classified by IARC in Group 3 (not classifiable as to its carcinogenicity to humans). High ingested-doses induce acute symptoms including kidney alterations, ulceration, convulsions, pulmonary congestion, edema, GIT disturbances, inflammation, and vomiting (WHO 1998).

PAT and intestinal epithelium

Ingestion of PAT leads to intestinal disorders, and, in children, outbreaks of diarrhea were attributed to the consumption of contaminated fruits (Lewis, Berg, and Kleine 1995). In rats, mice, and hamsters, PAT induced histopathological lesions in the GIT, including epithelial degeneration, hemorrhage, and ulceration of gastric mucosa, as well as exudation and epithelial desquamation in the duodenum (McKinley and Carlton 1980a; 1980b; McKinley, Carlton, and Boon 1982). A 24-hr exposure of proliferating Caco-

Table 6. Effects of aflatoxin B1 on intestinal epithelium and microbiota.

Intestinal partner	Experimental model	Conditions	Effects	References	
Epithelium	Human Caco-2 cells	150 μ M 24–72 h	Decrease in TEER Increase in DNA damage	(Gratz et al. 2007)	
		0.01–1 μ g/mL 24–72 h	Alterations of cell viability and growth Increase in DNA damage	(Zhang et al. 2015)	
	Broiler	Contaminated diet 4 mg/kg feed 21 days	Decrease in weight and length of the intestine Decrease in absorptive area	Decrease	(Ledoux et al. 1999)
		Contaminated diet 0.3 mg/kg feed 21 days	Increase in apoptosis of jejunal cells Increase in expression of <i>Bax</i> and <i>caspase-3</i> genes Decrease in expression of <i>Bcl2</i> gene	Increase in	(Peng et al. 2014)
		Contaminated diet 0.3 mg/kg feed 7–21 days	Decrease in jejunal villi height Decrease in PCNA positive proliferative cells Shedding of epithelial cells on the top of villi G2 cell cycle arrest	Decrease in	(Zhang et al. 2014)
	Rodent	Contaminated diet 0.07–0.75 mg/kg feed 28 days	No critical histological change		(Yunus et al. 2011)
		Intraperitoneal injection 2.5 mg/kg 3 days	Intestinal lesions in the duodenum and ileum and lymphocytic infiltration in intestinal tissues	Leucocytic	(Akinrinmade, Akinrinde, and Amid 2016)
Microbiota	Rat	Oral gavage 5–75 μ g/kg bw 4 weeks	Reduction in microbial diversity in the colon No change in the proportion of <i>Firmicutes</i> and <i>Bacteroidetes</i> Adverse effect on lactic acid bacteria	(Wang et al. 2016)	
		Broiler	Contaminated diet 1–2 mg/kg feed 21 days	Tenfold increase in facultative anaerobe bacteria (coliform) in the caecum Slight increase in total aerobic and lactic acid bacterial populations in the caecum	(Galarza-Seeber et al. 2016)

2 cells markedly decreased the number of cells and viability rate in a concentration-dependent manner due to necrosis but not apoptosis (Tannous et al. 2017). PAT-mediated acute toxicity on differentiated cells was partly due to destruction of TJ proteins and was associated with a reduction in TEER in human HT29 and Caco-2 cells without affecting intestinal absorption and secretion (Assunção et al. 2014; Mahfoud et al. 2002). In Caco-2 cells, Kawauchiya et al. (2011) suggested that the decrease in TEER was correlated with enhanced phosphorylation and subsequent degradation of ZO-1. In the same *in vitro* model, McLaughlin et al. (2009) reported a reduced expression of ZO-1 and occludin, which was accompanied by marked changes in the distribution but not levels of claudins. Translocation of noninvasive commensal *E. coli*, together with associated inflammatory responses, was also observed (Maresca et al. 2008). In rats, the influence of PAT on permeability, ion transport, and morphology in isolated colonic mucosa was assessed *ex vivo* (Mohan et al. 2012). High doses of PAT diminished TEER, elevated permeability to mannitol and induced pronounced morphologic effects including cell detachment, epithelial desquamation, and sub-mucosal swelling. For pig jejunal explants

exposed to lower doses of PAT, no significant differences were found in lesional scores and villi height (Maidana et al. 2016). According to Mahfoud et al. (2002), the toxicity attributed to PAT involved, among other potential mechanisms, inactivation of the active site of protein tyrosine phosphatases, which regulate the function of TJ proteins.

PAT and intestinal mucus

In a recent study, Maidana et al. (2016) investigated the impact of PAT exposure on intestinal mucus using pig jejunal explants. PAT significantly lowered number of goblet cells in both villi and crypts. No other apparent data are to date available on this mycotoxin. A summary of the influence of PAT on intestinal epithelium is presented in Table 7. To the best of our knowledge, there are no apparent data available to date on intestinal microbiota.

Table 7. Effects of patulin on intestinal epithelium and mucus.

Intestinal partner	Experimental model	Conditions	Effects	References
Epithelium	Human Caco-2 cells	1–150 µM 24 h	Concentration-dependent decrease in cell viability	(Assunção et al. 2016)
		0–100 µM 24 h	Decrease in cell viability	(Mahfoud et al. 2002)
		3–100 µM 5 or 24 h	Increase in cytotoxicity Increase in cell death	(Tannous et al. 2017)
		50 µM 72 h	Decrease in TEER Increased phosphorylation and degradation of ZO-1	(Kawauchiya et al. 2011)
		100 µM 5 h	Decrease in TEER Increase in permeability to FITC-dextran	(McLaughlin et al. 2009)
			Reduced expression of ZO-1 and occludin Changes in the distribution of claudins	
	Human HT29 cells	0–100 µM 24 h	Decrease in cell viability	(Mahfoud et al. 2002)
	Human HCT 116 cells	0–10 µM 24 h	Increase in cell apoptosis Increase in cleaved caspase 3 G2/M cell cycle arrest Increase in ROS production Increase in <i>ATF3</i> gene expression	(Kwon et al. 2012)
	Pig jejunal explants	10–30— 100 µM 4 h	No significant difference in lesional scores and villi height	(Maidana et al. 2016)
		100 µM 4 h	Increase in cell apoptosis	
Rat colonic explants	500 µM 24 h	Decrease in TEER Increase in permeability to mannitol Morphological alterations of the mucosa	(Mohan et al. 2012)	
Mucus	Pig jejunal explants	100 µM 4 h	Reduction in the number of goblet cells in villi and crypts	(Maidana et al. 2016)

Conclusions and next challenges for the future

Mycotoxins impair the integrity of intestinal epithelial barrier

Dietary exposure of humans and animals to mycotoxins is of growing concern due to their frequent prevalence in food and feed commodities (Streit et al. 2013). The intestinal mucosa is the first physical, chemical, and biological line of defense for the host and thus plays a critical role for maintaining intestinal homeostasis under mycotoxin-exposure stress. Evidence indicates that DON, ZEN, OTA, FB1, AFB1, and PAT when present individually markedly affects epithelial cells through various mechanisms as follows: (i) increase in cell death and cytotoxicity, (ii) enhanced permeability of the cell monolayer, (iii) decreased transepithelial electrical resistance (TEER), (iv) impaired expression, intracellular localization and function of TJ proteins, and (v) subsequent translocation of harmful stressors, in particular bacteria (commensals and pathogens), from gut lumen to internal environment. Due to these epithelium-targeted alterations, it is worthwhile to unravel the significance of mycotoxin exposure in the initiation of inflammatory reactions and clinical manifestations such as intestinal disorders. This is of utmost importance as, especially for DON, PAT, and ZEN, the differences between the health-based guidance values for mycotoxins, and their effective doses inducing effects on the intestine are lower than the usual safety factor of 100 (Maresca and Fantini 2010). Owing to apparent lactational transfer of various mycotoxins (Omar 2012) and, as already proposed by Akbari et al. (2017), evaluation of an early life exposure, associated to an immature intestinal barrier function, also warrants further attention.

Intestinal mucus and microbiota are emerging targets for mycotoxins

Even though the epithelial monolayer is a major functional element of the intestinal barrier, increasing evidence suggests that other constituents are involved such as mucus and microbiota, and these are emerging targets for mycotoxins. Regarding mucus, among the various mycotoxins

described in this review, DON is undoubtedly the most frequently documented. *In vivo*, DON toxicological impact on mucus has generally only been assessed through goblet cell number determination. The absence of a clear consensus concerning a deleterious or non-effect, viewed with respect to the sole “goblet cell number,” is at least to some extent due to differences in the experimental conditions used: intestinal region of interest, administration mode, and particularly duration, dose, frequency, and type of animal species (rodents, pig, chicken) which exhibit varying susceptibilities to mycotoxin exposure. In addition to this “goblet cell number” criterion, evaluation of the mycotoxins/mucus interplay through other various indicators such as mucin expression, mucin/mucus composition, mucin O-glycosylation, thickness, and physico-chemistry/penetrability of the mucus network also warrants special attention.

Concerning microbiota, few studies have to date been reported for all mycotoxins with demonstration of deleterious effects. However, especially during chronic exposure, the continuing presence of mycotoxins within the intestine may be considered to produce marked changes in the composition of microbiota, together with abundance and metabolic activity of specific groups or genera. Therefore, this area of research needs to be addressed further. In particular, one of the major challenges for the future might be to analyze mycotoxin-induced influence not only on fecal microbiota but also on mucosal microbiota, in close proximity to the epithelium or embedded within the mucus layer. Moreover, evaluating the variations of microbial functions such as signal transduction, metabolism, and transport of complex sugars and proteins, employing transcriptomics and/or metabolomics, might be a great opportunity to assess the impact of mycotoxins on health.

New mycotoxin-based associations may impair intestinal barrier integrity

New mycotoxins (emergent, modified and masked mycotoxins), as well as mycotoxin mixtures present in food and feed, warrant further attention. In particular, emergent mycotoxins, including beauvericin, enniatins, and alternariol (Gruber-Dorninger et al.

2016), and also modified forms of major mycotoxins such as the acetylated forms of DON (Payros et al. 2016) require to be carefully examined since these are known to induce adverse effects on intestinal functions. Similarly, simultaneous exposure to several mycotoxins may lead to additive, synergistic or antagonist toxic effects, which have been poorly evaluated through the prism of gut homeostasis (Alassane-Kpembi et al. 2015 ; 2017a).

Mycotoxins may compromise gut homeostasis by influencing crosstalk between epithelium, mucus, and microbiota

Another emerging challenge in the understanding of mycotoxin/intestinal barrier interplay is to take into account crosstalk between epithelium, mucus, and microbiota. As illustrated in Figure 1, these three gut players act not only as individual but also as tightly connected entities within the small intestine and colon to ensure host homeostasis. Regarding the epithelium/microbiota crosstalk, in various adult germ-free animal models such as rat, pig, or zebrafish, inoculation of complex

microbiota was shown to induce expression of genes involved in intestinal cell proliferation, differentiation, and mucus biosynthesis as well as in innate immune response and nutrient metabolism (Cheesman et al. 2011; Jones et al. 2007; Tomas et al. 2015). The role of specific bacteria was also assessed (Bry et al. 1996; Hooper et al. 1999). Reciprocally, the host epithelium may regulate and shape the microbiota, notably through Paneth-cell mediated secretion of antimicrobial peptides (Bevins and Salzman 2011).

Epithelium and mucus are also intrinsically connected components since enterocytes/colonocytes are interspersed by goblet cells all along the GIT. However, few studies to date investigated whether and how these constituents act in concert and are reciprocally regulated. The sole apparent study noted by Da Silva et al. (2014) occurred in rats subjected to chronic psychological stress. In an attempt to dissect the underlying “orchestrated” mechanisms, Lu et al. (2011) investigated colonic gene expression patterns of mucin Muc2 knockout ($Muc2^{-/-}$) mice. Expression of genes involved in cell structure related pathways was significantly

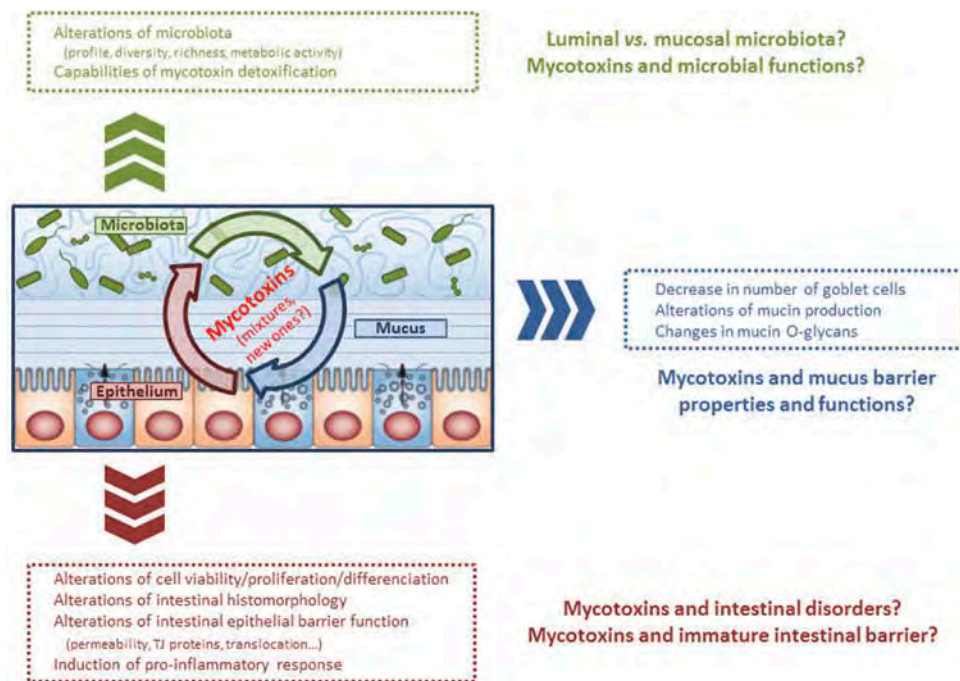


Figure 1. A schematic view of the three gut players involved in intestinal barrier integrity: example of the colon (adapted from Johansson, Sjövall, and Hansson 2013). The two-layered mucus with different properties is coloured in blue. The bacteria residing in the outer mucus layer are indicated in green. The epithelium (in red) combines colonocytes and mucin-secreting goblet cells. For each constituent, main findings on the effects of mycotoxins are summarized. These three constituents act not only as individual but also as tightly connected entities to ensure gut homeostasis. The consequences of mycotoxin exposure on this “orchestrated” triad should be evaluated as a challenging question for the future. Other questions to be addressed are also indicated.

altered. In particular, expression of genes regulating cell growth was enhanced in conjunction with increased crypt length and epithelial proliferation. Interestingly, the TJ-associated gene claudin-10 was upregulated, whereas claudin-1 and claudin-5 were downregulated.

Finally, concerning the mucus/microbiota interplay, the outer colonic mucus layer is the natural habitat for commensal bacteria (Johansson, Larsson, and Hansson 2011), due to the presence of mucin-derived carbohydrates that are utilized as an energy source (Bäckhed et al. 2005; El Kaoutari et al. 2013; Sonnenburg et al. 2005) or preferential binding sites through bacterial adhesins (Juge 2012). This may explain, at least to some extent, the regio-specific colonization of bacteria in the gut (Robbe et al. 2004). Specific bacterial mediators driving adhesion to mucins were identified, including pili (Le et al. 2013; Von Ossowski et al. 2010), mucus-binding proteins (MacKenzie et al. 2010), and other cell surface proteins (Pretzer et al. 2005). Numerous mucolytic bacteria have also been described (Tailford et al. 2015), such as *A. muciniphila* (Derrien et al. 2004), *Bacteroides thetaiotaomicron* (Bäckhed et al. 2005), *Bacteroides fragilis* (Huang, Lee, and Mazmanian 2011), *Ruminococcus gnavus* and *Ruminococcus torques* (Croston et al. 2013; Png et al. 2010). Some of these were suggested to be considered as biomarkers in gut health and disease (Everard et al. 2013; Malinen et al. 2010; Png et al. 2010). In particular, *A. muciniphila* prevents obesity and associated metabolic disorders, underlying the important crosstalk between host and “his” microbiota (Plovier et al. 2017). Further, Li et al. (2015) showed that bacterial species present in mucus exhibit differential proliferation and resource utilization compared to their counterparts in the lumen, and this is not restricted to mucolytic capability such as iron harvesting. Reciprocally, commensal bacteria may shape the mucus phenotype, as noted in rodents (Jakobsson et al. 2015; Johansson et al. 2015). The mucus/microbiota symbiotic system was recently expanded by identification of “sentinel” goblet cells in charge of protecting the colonic crypts from bacterial intruders that would have overwhelmed the inner mucus barrier (Birchenough et al. 2016).

All the issues raised here indicate the necessity to determine the deleterious effects of ingested mycotoxins on epithelium, mucus and microbiota, which are depicted as a “ménage à trois”, in which

each component interacts with each other. In conclusion, a broad range of questions and future challenges still need to be addressed for a healthy gut by improving risk assessment for exposure of humans and animals to dietary mycotoxins.

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Declaration of interest

The authors report no conflicts of interest.

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References

- Afriyie-Gyawu, E., M. C. Wiles, H. J. Huebner, M. B. Richardson, C. Fickey, and T. D. Phillips. 2005. Prevention of zearalenone-induced hyperestrogenism in prepubertal mice. *Journal of Toxicology and Environmental Health. Part A* 68:353–68.
- Akbari, P., S. Braber, H. Gremmels, P. J. Koelink, K. A. T. Verheijden, J. Garssen, and J. Fink-Gremmels. 2014. Deoxynivalenol: A trigger for intestinal integrity breakdown. *FASEB Journal* 28:2414–29.
- Akbari, P., S. Braber, S. Varasteh, A. Alizadeh, J. Garssen, and J. Fink-Gremmels. 2017. The intestinal barrier as an emerging target in the toxicological assessment of mycotoxins. *Archives of Toxicology*. in press. doi:10.1007/s00204-016-1794-8.
- Akinrinmade, F. J., A. S. Akinrinde, and A. Amid. 2016. Changes in serum cytokine levels, hepatic and intestinal morphology in aflatoxin B1-induced injury: Modulatory roles of melatonin and flavonoid-rich fractions from *Chromola odorata*. *Mycotoxin Research* 32:53–60.
- Alassane-Kpembi, I., O. Puel, and I. P. Oswald. 2015. Toxicological interactions between the mycotoxins deoxynivalenol, nivalenol and their acetylated derivatives in intestinal epithelial cells. *Archives of Toxicology* 89:1337–46.
- Alassane-Kpembi, I., O. Puel, P. Pinton, A. M. Cossalter, T. C. Chou, and I. P. Oswald. 2017b. Co-exposure to low doses of the food contaminants deoxynivalenol and nivalenol has a synergistic inflammatory effect on intestinal explants. *Archives of Toxicology*. in press. doi:10.1007/s00204-016-1902-9.

- Alassane-Kpembé, I., G. Schatzmayr, I. Taranu, D. Marin, O. Puel, and I. P. Oswald. 2017a. Mycotoxins co-contamination: Methodological aspects and biological relevance of combined toxicity studies. *Critical Reviews in Food Science and Nutrition* 16: 3489–3507. doi:10.1080/10408398.2016.1140632.
- Albenberg, L., T. V. Esipova, C. P. Judge, K. Bittinger, J. Chen, A. Laughlin, S. Grunberg, R. N. Baldassano, J. D. Lewis, H. Li, S. R. Thom, F. D. Bushman, S. A. Vinogradov, and G. D. Wu. 2014. Correlation between intraluminal oxygen gradient and radial partitioning of intestinal microbiota. *Gastroenterology* 147:1055–63.
- Ambort, D., M. E. V. Johansson, J. K. Gustafsson, H. E. Nilsson, A. Ermund, B. R. Johansson, P. J. B. Koeck, H. Hebert, and G. C. Hansson. 2012. Calcium and pH-dependent packing and release of the gel-forming MUC2 mucin. *Proceedings Natural Academic Sciences USA* 109:5645–50.
- Andretta, I., M. Kipper, C. R. Lehnen, L. Hauschild, M. M. Vale, and P. A. Lovatto. 2011. Meta-analytical study of productive and nutritional interactions of mycotoxins in broilers. *Poultry Science* 90:1934–40.
- Andretta, I., M. Kipper, C. R. Lehnen, L. Hauschild, M. M. Vale, and P. A. Lovatto. 2012. Meta-analytical study of productive and nutritional interactions of mycotoxins in growing pigs. *Animal* 6:1476–82.
- Antonissen, G., F. Van Immerseel, F. Pasmans, R. Ducatelle, G. P. J. Janssens, S. De Baere, K. C. Mountzouris, S. Su, E. A. Wong, B. De Meulenaer, M. Verlinden, M. Devreese, F. Haesebrouck, B. Novak, I. Dohnal, A. Martel, and S. Croubels. 2015. Mycotoxins deoxynivalenol and fumonisins alter the extrinsic component of intestinal barrier in broiler chickens. *Journal of Agricultural and Food Chemistry* 63:10846–55.
- Assunção, R., P. Alvito, C. R. Kleiveland, and T. E. Lea. 2016. Characterization of in vitro effects of patulin on intestinal epithelial and immune cells. *Toxicology Letters* 250–251:47–56.
- Assunção, R., M. Ferreira, C. Martins, I. Diaz, B. Padilla, D. Dupont, M. Braganca, and P. Alvito. 2014. Applicability of in vitro methods to study patulin bioaccessibility and its effects on intestinal membrane integrity. *Journal Toxicology Environment Health A* 77:983–92.
- Atuma, C., V. Strugala, A. Allen, and L. Holm. 2001. The adherent gastrointestinal mucus gel layer: Thickness and physical state in vivo. *American Journal Physiological Gastrointestinal Liver Physiological* 280:G922–G929.
- Azziz-Baumgartner, E., K. Lindblade, K. Gieseke, H. S. Rogers, S. Kieszak, H. Njapau, R. Schleicher, L. F. McCoy, A. Misore, K. DeCock, C. Rubin, and L. Slutsker. 2005. Case-control study of an acute aflatoxicosis outbreak, Kenya, 2004. *Environment Health Perspectives* 113:1779–83.
- Bäckhed, F., R. E. Ley, J. L. Sonnenburg, D. A. Peterson, and J. I. Gordon. 2005. Host-bacterial mutualism in the human intestine. *Science* 307:1915–20.
- Bailey, M. T., S. E. Dowd, N. M. A. Parry, J. D. Galley, D. B. Schauer, and M. Lyte. 2010. Stressor exposure disrupts commensal microbial populations in the intestines and leads to increased colonization by *Citrobacter rodentium*. *Infection and Immunity* 78:1509–19.
- Basso, K., F. Gomes, and A. P. L. Bracarense. 2013. Deoxynivalenol and fumonisin, alone or in combination, induce changes on intestinal junction complexes and in E-cadherin expression. *Toxins* 5:2341–52.
- Bennett, J. W., and M. Klich. 2003. Mycotoxins. *Clinical Microbiology Reviews* 16:497–516.
- Bevins, C. L., and N. H. Salzman. 2011. Paneth cells, antimicrobial peptides and maintenance of intestinal homeostasis. *Nature Reviews Microbiology* 9:356–68.
- Birchenough, G. M., E. E. Nystrom, M. E. Johansson, and G. C. Hansson. 2016. A sentinel goblet cell guards the colonic crypt by triggering Nlrp6-dependent Muc2 secretion. *Science* 352:1535–42.
- Bondy, G. S., and J. J. Pestka. 2000. Immunomodulation by fungal toxins. *Journal Toxicological Environment Health B* 3:109–43.
- Bouhet, S., E. Hourcade, N. Loiseau, A. Fikry, S. Martinez, M. Roselli, P. Galtier, E. Mengheri, and I. P. Oswald. 2004. The mycotoxin fumonisin B1 alters the proliferation and the barrier function of porcine intestinal epithelial cells. *Toxicological Sciences* 77:165–71.
- Bouhet, S., and I. P. Oswald. 2007. The intestine as a possible target for fumonisin toxicity. *Molecular Nutrition & Food Research* 51:925–31.
- Bracarense, A. P., J. Luciola, B. Grenier, G. Drociunas Pacheco, W. D. Moll, G. Schatzmayr, and I. P. Oswald. 2012. Chronic ingestion of deoxynivalenol and fumonisin, alone or in interaction, induces morphological and immunological changes in the intestine of piglets. *The British Journal of Nutrition* 107:1776–86.
- Brown, T. P., G. E. Rottinghaus, and M. E. Williams. 1992. Fumonisin mycotoxicosis in broilers: Performance and pathology. *Avian Diseases* 36:450–54.
- Bry, L., P. G. Falk, T. Midtvedt, and J. I. Gordon. 1996. A model of host-microbial interactions in an open mammalian ecosystem. *Science* 273:1380–83.
- Bryden, W. L. 2012. Mycotoxin contamination of the feed supply chain: Implications for animal productivity and feed security. *Animal Feed Sciences Technological* 173:134–58.
- Burel, C., M. Tanguy, P. Guerre, E. Boilletot, R. Cariolet, M. Queguiner, G. Postollec, P. Pinton, G. Salvat, I. P. Oswald, and P. Fravallo. 2013. Effect of low dose of fumonisins on pig health: Immune status, intestinal microbiota and sensitivity to *Salmonella*. *Toxins* 5:841–64.
- Burger-Van Paassen, N., A. Vincent, P. J. Puiman, M. Van Der Sluis, J. Bouma, G. Boehm, J. B. Van Goudoever, I. Van Seuning, and I. B. Renes. 2009. The regulation of intestinal mucin MUC2 expression by short-chain fatty acids: Implications for epithelial protection. *The Biochemical Journal* 420:211–19.
- Cano, P. M., J. Seeboth, F. Meurens, J. Cognie, R. Abrami, I. P. Oswald, and L. Guzylack-Piriou. 2013. Deoxynivalenol as a new factor in the persistence of intestinal inflammatory diseases: An emerging hypothesis through possible modulation of Th17-mediated response. *Plos One* 8: e53647.

- Casado, J. M., M. Theumer, D. T. Masih, S. Chulze, and H. R. Rubinstein. 2001. Experimental subchronic mycotoxicoses in mice: Individual and combined effects of dietary exposure to fumonisins and aflatoxin B1. *Food and Chemical Toxicology* 39:579–86.
- Cheat, S., P. Pinton, A. M. Cossalter, J. Cagnie, M. Vilariño, P. Callu, I. Raymond-Letron, I. P. Oswald, and M. Kolf-Clauw. 2016. The mycotoxins deoxynivalenol and nivalenol show in vivo synergism on jejunum enterocytes apoptosis. *Food and Chemical Toxicology* 87:45–54.
- Cheesman, S. E., J. T. Neal, E. Mittge, B. M. Sereidick, and K. Guillemin. 2011. Epithelial cell proliferation in the developing zebrafish intestine is regulated by the Wnt pathway and microbial signaling via Myd88. *Proceedings National Academy Sciences USA* 108:4570–77.
- Clark, H. A., and S. M. Snedeker. 2006. Ochratoxin A: Its cancer risk and potential for exposure. *Journal Toxicological Environment Health B* 9:265–96.
- Crosnier, C., D. Stamataki, and J. Lewis. 2006. Organizing cell renewal in the intestine: Stem cells, signals and combinatorial control. *Nature Reviews Genetics* 7:349–59.
- Crost, E. H., L. E. Tailford, G. Le Gall, M. Fons, B. Henrissat, and N. Juge. 2013. Utilisation of mucin glycans by the human gut symbiont *Ruminococcus gnavus* is strain-dependent. *Plos One* 8:e76341.
- Cui, J., L. Xing, Z. Li, S. Wu, J. Wang, J. Liu, J. Wang, X. Yan, and X. Zhang. 2010. Ochratoxin A induces G(2) phase arrest in human gastric epithelium GES-1 cells in vitro. *Toxicology Letters* 193:152–58.
- Da Silva, S., C. Robbe-Masselot, A. Ait-Belgnaoui, A. Mancuso, M. Mercade-Loubière, C. Salvador-Cartier, M. Gillet, L. Ferrier, P. Loubière, E. Dague, V. Theodorou, et M. Mercier-Bonin. 2014. Stress disrupts intestinal mucus barrier in rats via mucin O-glycosylation shift: Prevention by a probiotic treatment. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 307:G420–G429.
- Davenport, E. R., O. Mizrahi-Man, K. Michelini, L. B. Barreiro, C. Ober, and Y. Gilad. 2014. Seasonal variation in human gut microbiome composition. *Plos One* 9:e90731.
- De Vos, W. M. 2015. Microbial biofilms and the human intestinal microbiome. *NPJ Biofilms Microbiomes* 1:15005.
- Derrien, M., E. E. Vaughan, C. M. Plugge, and W. M. De Vos. 2004. *Akkermansia muciniphila* gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. *International Journal of System Evolution Microbiology* 54:1469–76.
- Diesing, A. K., C. Nossol, S. Danicke, N. Walk, A. Post, S. Kahlert, H. J. Rothkotter, and J. Kluess. 2011. Vulnerability of polarised intestinal porcine epithelial cells to mycotoxin deoxynivalenol depends on the route of application. *Plos One* 6:e17472.
- Donaldson, G. P., S. M. Lee, and S. K. Mazmanian. 2015. Gut biogeography of the bacterial microbiota. *Nature Reviews Microbiology* 14:20–32.
- Donohoe, D. R., N. Garge, X. Zhang, W. Sun, T. M. O’Connell, M. K. Bunger, and S. J. Bultman. 2011. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. *Cell Metabolism* 13:517–26.
- Eckburg, P. B., E. M. Bik, C. N. Bernstein, E. Purdom, L. Dethlefsen, M. Sargent, S. R. Gill, K. E. Nelson, and D. A. Relman. 2005. Diversity of the human intestinal microbial flora. *Science* 308:1635–38.
- El Kaoutari, A., F. Armougom, J. I. Gordon, D. Raoult, and B. Henrissat. 2013. The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. *Nature Reviews Microbiology* 11:497–504.
- Ermund, A., A. Schütte, M. E. V. Johansson, J. K. Gustafsson, G. C. Hansson, and A. Schuette. 2013. Gastrointestinal mucus layers have different properties depending on location - 1. Studies of mucus in mouse stomach, small intestine, Peyer’s patches and colon. *American Journal of Physiology. Gastrointestinal and Liver Physiology* 305: G341–G347.
- Everard, A., C. Belzer, L. Geurts, J. P. Ouwerkerk, C. Druart, L. B. Bindels, Y. Guiot, M. Derrien, G. G. Muccioli, N. M. Delzenne, W. M. De Vos, and P. D. Cani. 2013. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proceedings National Academy Sciences USA* 110:9066–71.
- Föllmann, W., N. Ali, M. Blaszkewicz, and G. H. Degen. 2016. Biomonitoring of mycotoxins in urine: Pilot study in mill workers. *Journal of Toxicology and Environmental Health. Part A* 79:1015–25.
- Fuchs, E., E. M. Binder, D. Heidler, and R. Krska. 2002. Structural characterization of metabolites after the microbial degradation of type A trichothecenes by the bacterial strain BBSH 797. *Food Additives and Contaminants* 19:379–86.
- Galarza-Seeber, R., J. D. Latorre, L. R. Bielke, V. A. Kuttappan, A. D. Wolfenden, X. Hernandez-Velasco, R. Merino-Guzman, J. L. Vicente, A. Donoghue, D. Cross, B. M. Hargis, and G. Tellez. 2016. Leaky gut and mycotoxins: Aflatoxin B1 does not increase gut permeability in broiler chickens. *Frontiers Veterinary Sciences* 3:10.
- Ghareeb, K., W. A. Awad, J. Böhm, and Q. Zebeli. 2015. Impacts of the feed contaminant deoxynivalenol on the intestine of monogastric animals: Poultry and swine. *Journal of Applied Toxicology* 35:327–37.
- Glaser, N., and H. Stopper. 2012. Patulin: Mechanism of genotoxicity. *Food and Chemical Toxicology* 50:1796–801.
- Gourbeyre, P., M. Berri, Y. Lippi, F. Meurens, S. Vincent-Naulleau, J. Laffitte, C. Rogel-Gaillard, P. Pinton, and I. P. Oswald. 2015. Pattern recognition receptors in the gut: Analysis of their expression along the intestinal tract and the crypt/villus axis. *Physiological Reports* 3:e12225.
- Gratz, S., Q. K. Wu, H. El-Nezami, R. O. Juvonen, H. Mykkänen, and P. C. Turner. 2007. *Lactobacillus rhamnosus* strain GG reduces aflatoxin B1 transport, metabolism, and toxicity in Caco-2 cells. *Applied and Environmental Microbiology* 73:3958–64.
- Gratz, S. W., G. Duncan, and A. J. Richardson. 2013. The human fecal microbiota metabolizes deoxynivalenol and deoxynivalenol-3-glucoside and may be responsible for

- urinary deepoxy-deoxynivalenol. *Applied and Environmental Microbiology* 79:1821–25.
- Grenier, B., and T. J. Applegate. 2013. Modulation of intestinal functions following mycotoxin ingestion: Meta-analysis of published experiments in animals. *Toxins* 5:396–430.
- Grenier, B., A.-P. F. L. Bracarense, H. E. Schwartz, C. Trumel, A.-M. Cossalter, G. Schatzmayr, M. Kolf-Clauw, W.-D. Moll, and I. P. Oswald. 2012. The low intestinal and hepatic toxicity of hydrolyzed fumonisin B₁ correlates with its inability to alter the metabolism of sphingolipids. *Biochemical Pharmacology* 83:1465–73.
- Gruber-Dorninger, C., B. Novak, V. Nagl, and F. Berthiller. 2016. Emerging mycotoxins: Beyond traditionally determined food contaminants. *Journal of Agricultural and Food Chemistry*. doi:10.1021/acs.jafc.6b03413.
- Gu, S., D. Chen, J.-N. Zhang, X. Lv, K. Wang, L.-P. Duan, Y. Nie, and X.-L. Wu. 2013. Bacterial community mapping of the mouse gastrointestinal tract. *Plos One* 8:e74957.
- Guo, M., K. Huang, S. Chen, X. Qi, X. He, W.-H. Cheng, Y. Luo, K. Xia, and W. Xu. 2014. Combination of metagenomics and culture-based methods to study the interaction between ochratoxin A and gut microbiota. *Toxicological Sciences* 141:314–23.
- Hamer, H. M., D. Jonkers, K. Venema, S. Vanhoutvin, F. J. Troost, and R. J. Brummer. 2008. Review article: The role of butyrate on colonic function. *Alimentary Pharmacology & Therapeutics* 27:104–19.
- Hansson, G. C., and M. E. V. Johansson. 2010. The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. *Gut Microbes* 1:51–54.
- Hara-Kudo, Y., Y. Sugita-Konishi, F. Kasuga, and S. Kumagai. 1996. Effects of deoxynivalenol on *Salmonella enteritidis* infection. *Mycotoxins* 42:51–55.
- He, J., and T. Zhou. 2010. Patented techniques for detoxification of mycotoxins in feeds and food matrices. *Recent Patents Food, Nutritional Agricultural* 2:96–104.
- Hedman, R., and H. Pettersson. 1997. Transformation of nivalenol by gastrointestinal microbes. *Arch Tierernährung* 50:321–29.
- Hooper, L. V., J. Xu, P. G. Falk, T. Midtvedt, and J. I. Gordon. 1999. A molecular sensor that allows a gut commensal to control its nutrient foundation in a competitive ecosystem. *Proceedings Natural Academic Sciences USA* 96:9833–38.
- Huang, J. Y., S. M. Lee, and S. K. Mazmanian. 2011. The human commensal *Bacteroides fragilis* binds intestinal mucin. *Anaerobe* 17:137–41.
- Jakhar, K. K., and J. R. Sadana. 2004. Sequential pathology of experimental aflatoxicosis in quail and the effect of selenium supplementation in modifying the disease process. *Mycopathologia* 157:99–109.
- Jakobsson, H. E., A. M. Rodríguez-Piñeiro, A. Schütte, A. Ermund, P. Boysen, M. Bemark, F. Sommer, F. Bäckhed, G. C. Hansson, and M. E. Johansson. 2015. The composition of the gut microbiota shapes the colon mucus barrier. *EMBO Reports* 16:164–77.
- Jia, X., J. Cui, X. Meng, L. Xing, H. Shen, J. Wang, J. Liu, Y. Wang, W. Lian, and X. Zhang. 2016. Malignant transformation of human gastric epithelium cells via reactive oxygen species production and Wnt/ β -catenin pathway activation following 40-week exposure to ochratoxin A. *Cancer Letters* 372:36–47.
- Johansson, M. E. V. 2012. Fast renewal of the distal colonic mucus layers by the surface goblet cells as measured by in vivo labeling of mucin glycoproteins. *Plos One* 7:e41009.
- Johansson, M. E. V., J. K. Gustafsson, J. Holmén-Larsson, K. S. Jabbar, L. Xia, H. Xu, F. K. Ghishan, F. A. Carvalho, A. T. Gewirtz, H. Sjövall, and G. C. Hansson. 2014. Bacteria penetrate the normally impenetrable inner colon mucus layer in both murine colitis models and patients with ulcerative colitis. *Gut* 63:281–91.
- Johansson, M. E. V., H. E. Jakobsson, J. Holmén-Larsson, A. Schütte, A. Ermund, A. M. Rodríguez-Piñeiro, L. Arike, C. Wising, F. Svensson, F. Bäckhed, and G. C. Hansson. 2015. Normalization of host intestinal mucus layers requires long-term microbial colonization. *Cell Host & Microbe* 18:582–92.
- Johansson, M. E. V., J. M. H. Larsson, and G. C. Hansson. 2011. The two mucus layers of colon are organized by the MUC2 mucin, whereas the outer layer is a legislator of host-microbial interactions. *Proceedings Natural Academic Sciences USA* 108:4659–65.
- Johansson, M. E. V., M. Phillipson, J. Petersson, A. Velcich, L. Holm, and G. C. Hansson. 2008. The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. *Proceedings Natural Academic Sciences USA* 108:4659–65.
- Johansson, M. E. V., H. Sjövall, and G. C. Hansson. 2013. The gastrointestinal mucus system in health and disease. *Natural Reviews Gastroenterology Hepatology* 10:352–61.
- Jones, S. A., F. Z. Chowdhury, A. J. Fabich, A. Anderson, D. M. Schreiner, A. L. House, S. M. Autieri, M. P. Leatham, J. J. Lins, M. Jorgensen, P. S. Cohen, and T. Conway. 2007. Respiration of *Escherichia coli* in the mouse intestine. *Infection and Immunity* 75:4891–99.
- Juge, N. 2012. Microbial adhesins to gastrointestinal mucus. *Trends in Microbiology* 20:30–39.
- Kana, J. R., A. Tegua, B. M. Mungfu, and J. Tchoumboue. 2011. Growth performance and carcass characteristics of broiler chickens fed diets supplemented with graded levels of charcoal from maize cob or seed of *Canarium schweinfurthii*. *Trop Animal Health Product* 43:51–56.
- Karlovsy, P., M. Suman, F. Berthiller, J. De Meester, G. Eisenbrand, I. Perrin, I. P. Oswald, G. Speijers, A. Chiodini, T. Recker, and P. Dussort. 2016. Impact of food processing and detoxification treatments on mycotoxin contamination. *Mycotoxin Research* 32:179–205.
- Kasuga, F., Y. Hara-Kudo, N. Saito, S. Kumagai, and Y. Sugita-Konishi. 1998. *In vitro* effect of deoxynivalenol on the differentiation of human colonic cell lines Caco-2 and T84. *Mycopathologia* 142:161–67.
- Kawauchiya, T., R. Takumi, Y. Kudo, A. Takamori, T. Sasagawa, K. Takahashi, and H. Kikuchi. 2011.

- Correlation between the destruction of tight junction by patulin treatment and increase of phosphorylation of ZO-1 in Caco-2 human colon cancer cells. *Toxicology Letters* 205:196–202.
- Khlangwiset, P., G. S. Shephard, and F. Wu. 2011. Aflatoxins and growth impairment: A review. *Critical Reviews in Toxicology* 41:740–55.
- Koh, A., F. De Vadder, P. Kovatcheva-Datchary, and F. Bäckhed. 2016. From dietary fiber to host physiology: Short-chain fatty acids as key bacterial metabolites. *Cell* 165:1332–45.
- Kószegi, T., and M. Poór. 2016. Ochratoxin A: Molecular interactions, mechanisms of toxicity and prevention at the molecular level. *Toxins* 8:111.
- Kouadio, J. H., T. A. Mobio, I. Baudrimont, S. Moukha, S. D. Dano, and E. E. Creppy. 2005. Comparative study of cytotoxicity and oxidative stress induced by deoxynivalenol, zearalenone or fumonisin B1 in human intestinal cell line Caco-2. *Toxicology* 213:56–65.
- Kowalska, K., D. E. Habrowska-Górczyńska, and A. W. Piastowska-Ciesielska. 2016. Zearalenone as an endocrine disruptor in humans. *Environmental Toxicology and Pharmacology* 48:141–49.
- Kwon, O., N. K. Soung, N. R. Thimmegowda, S. J. Jeong, J. H. Jang, D.-O. Moon, J. K. Chung, K. S. Lee, Y. T. Kwon, R. L. Erikson, J. S. Ahn, and B. Y. Kim. 2012. Patulin induces colorectal cancer cells apoptosis through EGR-1 dependent ATF3 up-regulation. *Cellular Signalling* 24:943–50.
- Lallès, J. P., M. Lessard, and G. Boudry. 2009. Intestinal barrier function is modulated by short-term exposure to fumonisin B(1) in Ussing chambers. *Veterinary Research Communications* 33:1039–43.
- Lallès, J. P., M. Lessard, I. P. Oswald, and J. C. David. 2010. Consumption of fumonisin B1 for 9 days induces stress proteins along the gastrointestinal tract of pigs. *Toxicol* 55:244–49.
- Lambert, D., P. J. Padfield, J. McLaughlin, S. Cannell, and C. A. O'Neill. 2007. Ochratoxin A displaces claudins from detergent resistant membrane microdomains. *Biochemical and Biophysical Research Communications* 358:632–36.
- Larsson, J. M. H., H. Karlsson, H. Sjövall, and G. C. Hansson. 2009. A complex, but uniform O-glycosylation of the human MUC2 mucin from colonic biopsies analyzed by nanoLC/MSn. *Glycobiology* 19:756–66.
- Le, D. T. L., T. L. Tran, M.-P. Duviau, M. Meyrand, Y. Guérardel, M. Castelain, P. Loubière, M.-P. Chapot-Chartier, E. Dague, and M. Mercier-Bonin. 2013. Unraveling the role of surface mucus-binding protein and pili in muco-adhesion of *Lactococcus lactis*. *Plos One* 8:e79850.
- Lebrun, B., C. Tardivel, B. Félix, A. Abysique, J. D. Troadec, S. Gaigé, and M. Dallaporta. 2015. Dysregulation of energy balance by trichothecene mycotoxins: Mechanisms and prospects. *Neurotoxicology* 49:15–27.
- Ledoux, D. R., G. E. Rottinghaus, A. J. Bermudez, and M. Alonso-Debolt. 1999. Efficacy of a hydrated sodium calcium aluminosilicate to ameliorate the toxic effects of aflatoxin in broiler chicks. *Poultry Science* 78:204–10.
- Lee, S. C., J. T. Beery, and F. S. Chu. 1984. Immunohistochemical fate of ochratoxin A in mice. *Toxicology and Applied Pharmacology* 72:218–27.
- Lessard, M., G. Boudry, B. Sève, I. P. Oswald, and J.-P. Lallès. 2009. Intestinal physiology and peptidase activity in male pigs are modulated by consumption of corn culture extracts containing fumonisins. *The Journal of Nutrition* 139:1303–07.
- Lewczuk, B., B. Przybylska-Gornowicz, M. Gajecka, K. Targonska, N. Ziolkowska, M. Prusik, and M. Gajecki. 2016. Histological structure of duodenum in gilts receiving low doses of zearalenone and deoxynivalenol in feed. *Experimental and Toxicologic Pathology* 68:157–66.
- Lewis, S. A., J. R. Berg, and T. J. Kleine. 1995. Modulation of epithelial permeability by extracellular macromolecules. *Physiological Reviews* 75:561–89.
- Ley, R. E., M. Hamady, C. Lozupone, P. J. Turnbaugh, R. R. Ramey, J. S. Bircher, M. L. Schlegel, T. A. Tucker, M. D. Schrenzel, R. Knight, and J. I. Gordon. 2008. Evolution of mammals and their gut microbes. *Science* 320:1647–51.
- Li, H., J. P. Limenitakis, T. Fuhrer, M. B. Geuing, M. A. Lawson, M. Wyss, S. Brugiroux, I. Keller, J. A. Macpherson, S. Rupp, B. Stolp, J. V. Stein, B. Stecher, U. Sauer, K. D. McCoy, and A. J. Macpherson. 2015. The outer mucus layer hosts a distinct intestinal microbial niche. *Nature Communications* 6:8292.
- Linden, S. K., P. Sutton, N. G. Karlsson, V. Korolik, and M. A. McGuckin. 2008. Mucins in the mucosal barrier to infection. *Mucosal Immunology* 1:183–97.
- Liu, J., S. Wu, H. Shen, J. Cui, Y. Wang, L. Xing, J. Wang, X. Yan, and X. Zhang. 2015. Ochratoxin A induces DNA damage and G2 phase arrest in human esophageal epithelium Het-1A cells in vitro. *The Journal of Toxicological Sciences* 40:657–65.
- Loiseau, N., L. Debrauwer, T. Sambou, S. Bouhet, J. D. Miller, P. G. Martin, J.-L. Viadère, P. Pinton, O. Puel, T. Pineau, J. Tulliez, P. Galtier, and I. P. Oswald. 2007. Fumonisin B1 exposure and its selective effect on porcine jejunal segment: Sphingolipids, glycolipids and trans-epithelial passage disturbance. *Biochemical Pharmacology* 74:144–52.
- Louis, P., G. L. Hold, and H. J. Flint. 2014. The gut microbiota, bacterial metabolites and colorectal cancer. *Nature Reviews Microbiology* 12:661–72.
- Louis, P., P. Young, G. Holtrop, and H. J. Flint. 2010. Diversity of human colonic butyrate-producing bacteria revealed by analysis of the butyryl-CoA: AcetateCoA-transferase gene. *Environmental Microbiology* 12:304–14.
- Lozupone, C. A., J. I. Stombaugh, J. I. Gordon, J. K. Jansson, and R. Knight. 2012. Diversity, stability and resilience of the human gut microbiota. *Nature* 489:220–30.
- Lu, P., N. Burger-Van Paassen, M. Van Der Sluis, J. Witte-Bouma, J. P. Kerckaert, J. B. Van Goudoever, I. Van Seuningen, and I. B. Renes. 2011. Colonic gene expression patterns of mucin muc2 knockout mice reveal various phases in colitis development. *Inflammatory Bowel Diseases* 17:2047–57.
- Lucioli, J., P. Pinton, P. Callu, J. Laffitte, F. Grosjean, M. Kolf-Claw, I. P. Oswald, and A. P. Bracarense. 2013. The food

- contaminant deoxynivalenol activates the mitogen activated protein kinases in the intestine: Interest of ex vivo models as an alternative to in vivo experiments. *Toxicol* 66:31–36.
- MacKenzie, D. A., F. Jeffers, M. L. Parker, A. Vibert-Vallet, R. J. Bongaerts, S. Roos, J. Walter, and N. Juge. 2010. Strain-specific diversity of mucus-binding proteins in the adhesion and aggregation properties of *Lactobacillus reuteri*. *Microbiology* 156:3368–78.
- Mahfoud, R., M. Maresca, N. Garmy, and J. Fantini. 2002. The mycotoxin patulin alters the barrier function of the intestinal epithelium: Mechanism of action of the toxin and protective effects of glutathione. *Toxicology and Applied Pharmacology* 181:209–18.
- Maidana, L., J. R. Gerez, R. El Khoury, F. Pinho, O. Puel, I. P. Oswald, and A. P. Bracarense. 2016. Effects of patulin and ascladiol on porcine intestinal mucosa: An ex vivo approach. *Food and Chemical Toxicology* 98:189–94.
- Malinen, E., L. Krogus-Kurikka, A. Lyra, J. Nikkilä, A. Jääskeläinen, T. Rinttilä, T. Vilpponen-Salmela, A. J. Von Wright, and A. Palva. 2010. Association of symptoms with gastrointestinal microbiota in irritable bowel syndrome. *World Journal of Gastroenterology* 16:4532–40.
- Marasas, W. F. 2001. Discovery and occurrence of the fumonisins: A historical perspective. *Environment Health Perspectives* 109:239–43.
- Maresca, M. 2013. From the gut to the brain: Journey and pathophysiological effects of the food-associated trichothecene mycotoxin deoxynivalenol. *Toxins* 5:784–820.
- Maresca, M., and J. Fantini. 2010. Some food-associated mycotoxins as potential risk factors in humans predisposed to chronic intestinal inflammatory diseases. *Toxicol* 56:282–94.
- Maresca, M., R. Mahfoud, A. Pfohl-Leszkowicz, and J. Fantini. 2001. The mycotoxin ochratoxin A alters intestinal barrier and absorption functions but has no effect on chloride secretion. *Toxicology and Applied Pharmacology* 176:54–63.
- Maresca, M., N. Yahi, L. Younes-Sakr, M. Boyron, B. Caporiccio, and J. Fantini. 2008. Both direct and indirect effects account for the pro-inflammatory activity of enteropathogenic mycotoxins on the human intestinal epithelium: Stimulation of interleukin-8 secretion, potentiation of interleukin-1 β effect and increase in the transepithelial passage of commensal bacteria. *Toxicology and Applied Pharmacology* 228:84–92.
- Marin, D., M. Motiu, and I. Taranu. 2015. Food contaminant zearalenone and its metabolites affect cytokine synthesis and intestinal epithelial integrity of porcine cells. *Toxins* 7:1979–88.
- Maurice, C. F., H. J. Haiser, and P. J. Turnbaugh. 2013. Xenobiotics shape the physiology and gene expression of the active human gut microbiome. *Cell* 152:39–50.
- McKinley, E. R., and W. W. Carlton. 1980a. Patulin mycotoxicosis in Swiss ICR mice. *Food and Cosmetics Toxicology* 18:181–87.
- McKinley, E. R., and W. W. Carlton. 1980b. Patulin mycotoxicosis in the Syrian hamster. *Food and Cosmetics Toxicology* 18:173–79.
- McKinley, E. R., W. W. Carlton, and G. D. Boon. 1982. Patulin mycotoxicosis in the rat: Toxicology, pathology and clinical pathology. *Food and Chemical Toxicology* 20:289–300.
- McLaughlin, J., P. J. Padfield, J. P. H. Burt, and C. A. O'Neill. 2004. Ochratoxin A increases permeability through tight junctions by removal of specific claudin isoforms. *American Journal Physiological Cellular Physiological* 287: C1412–C1417.
- McLaughlin, J., P. J. Padfield, J. P. H. Burt, and C. A. O'Neill. 2009. The mycotoxin patulin, modulates tight junctions in Caco-2 cells. *Toxicol In Vitro* 23:83–89.
- Minervini, F., A. Garbetta, I. D'Antuono, A. Cardinali, N. A. Martino, L. Debellis, and A. Visconti. 2014. Toxic mechanisms induced by fumonisin B1 mycotoxin on human intestinal cell line. *Archives of Environmental Contamination and Toxicology* 67:115–23.
- Mohan, H. M., D. Collins, S. Maher, E. G. Walsh, D. C. Winter, P. J. O'Brien, D. J. Brayden, and A. W. Baird. 2012. The mycotoxin patulin increases colonic epithelial permeability in vitro. *Food and Chemical Toxicology* 50:4097–102.
- Nava, G. M., H. J. Friedrichsen, and T. S. Stappenbeck. 2011. Spatial organization of intestinal microbiota in the mouse ascending colon. *The ISME Journal* 5:627–38.
- Norred, W. P. 1993. Fumonisins-mycotoxins produced by *fusarium moniliforme*. *Journal of Toxicology and Environmental Health. Part A* 38:309–28.
- Ok, H. E., H. J. Kim, T. Y. Cho, K. S. Oh, and H. S. Chun. 2009. Determination of deoxynivalenol in cereal-based foods and estimation of dietary exposure. *Journal of Toxicology and Environmental Health. Part A* 72:1424–30.
- Omar, S. S. 2012. Incidence of aflatoxin M1 in human and animal milk in Jordan. *Journal of Toxicology and Environmental Health. Part A* 75:1404–09.
- Osselaere, A., R. Santos, V. Hautekiet, P. De Backer, K. Chiers, R. Ducatelle, and S. Croubels. 2013. Deoxynivalenol impairs hepatic and intestinal gene expression of selected oxidative stress, tight junction and inflammation proteins in broiler chickens, but addition of an adsorbing agent shifts the effects to the distal parts of the small intestine. *Plos One* 8:e69014.
- Ouwerkerk, J. P., W. M. De Vos, and C. Belzer. 2013. Glycobiome: Bacteria and mucus at the epithelial interface. *Best Practice & Research Clinical Gastroenterology* 27:25–38.
- Payros, D., I. Alassane-Kpembi, A. Pierron, N. Loiseau, P. Pinton, and I. P. Oswald. 2016. Toxicology of deoxynivalenol and its acetylated and modified forms. *Archives of Toxicology* 90:2931–57.
- Payros, D., U. Dobrindt, P. Martin, T. Secher, A. P. Bracarense, M. Boury, J. Laffitte, P. Pinton, E. Oswald, and I. P. Oswald. 2017. Food contaminant deoxynivalenol exacerbates the genotoxicity of gut microbiota. *Mbio* 8: e00007–17.

- Pédrón, T., C. Mulet, C. Dauga, L. Frangeul, C. Chervaux, G. Grompone, and P. J. Sansonetti. 2012. A crypt-specific core microbiota resides in the mouse colon. *Mbio* 3: e00116–12.
- Peng, X., K. Zhang, S. Bai, X. Ding, Q. Zeng, J. Yang, J. Fang, and K. Chen. 2014. Histological lesions, cell cycle arrest, apoptosis and T cell subsets changes of spleen in chicken fed aflatoxin-contaminated corn. *International Journal of Environmental Research and Public Health* 11:8567–80.
- Pestka, J. J. 2010. Deoxynivalenol: Mechanisms of action, human exposure, and toxicological relevance. *Archives of Toxicology* 84:663–79.
- Pestka, J. J., and A. T. Smolinski. 2005. Deoxynivalenol: Toxicology and potential effects on humans. *Journal of Toxicological Environment Health B* 8:39–69.
- Pfohl-Leszkowicz, A., and R. A. Manderville. 2007. Ochratoxin A: An overview on toxicity and carcinogenicity in animals and humans. *Molecular Nutrition & Food Research* 51:61–99.
- Pierron, A., S. Mimoun, L. S. Murate, N. Loiseau, Y. Lippi, A. P. Bracarense, G. Schatzmayr, F. Berthiller, W. D. Moll, and I. P. Oswald. 2016a. Intestinal toxicity of the masked mycotoxin deoxynivalenol-3- β -D-glucoside. *Archives of Toxicology* 90:2037–46.
- Pierron, A., S. Mimoun, L. S. Murate, N. Loiseau, Y. Lippi, A. P. Bracarense, G. Schatzmayr, J. W. He, T. Zhou, W. D. Moll, and I. P. Oswald. 2016b. Microbial biotransformation of DON: Molecular basis for reduced toxicity. *Scientific Reports* 6:29105.
- Pinto, M. J. D. V., J. M. Veiga, P. Fernandes, C. Ramos, S. Gonçalves, M. M. L. V. Velho, and J. S. Guerreiro. 2015. Airborne microorganisms associated with packaging glass sorting facilities. *Journal of Toxicology and Environmental Health. Part A* 78:685–96.
- Pinton, P., C. Braicu, J. P. Nougayrede, J. Laffitte, I. Taranu, and I. P. Oswald. 2010. Deoxynivalenol impairs porcine intestinal barrier function and decreases the protein expression of claudin-4 through a Mitogen-Activated Protein Kinase-dependent mechanism. *The Journal of Nutrition* 140:1956–62.
- Pinton, P., F. Graziani, A. Pujol, C. Nicoletti, O. Paris, P. Ernouf, E. Di Pasquale, J. Perrier, I. P. Oswald, and M. Maresca. 2015. Deoxynivalenol inhibits the expression by goblet cells of intestinal mucins through a PKR and MAP kinase dependent repression of the resistin-like molecule β . *Molecular Nutrition & Food Research* 59:1076–87.
- Pinton, P., J.-P. Nougayrède, J.-C. Del Rio, C. Moreno, D. E. Marin, L. Ferrier, A.-P. Bracarense, M. Kolf-Clauw, and I. P. Oswald. 2009. The food contaminant deoxynivalenol decreases intestinal barrier permeability and reduces claudin expression. *Toxicology and Applied Pharmacology* 237:41–48.
- Pinton, P., and I. P. Oswald. 2014. Effect of deoxynivalenol and other Type B trichothecenes on the intestine: A review. *Toxins* 6:1615–43.
- Pinton, P., D. Tsybulskyy, J. Luciola, J. Laffitte, P. Callu, F. Lyazhri, F. Grosjean, A. P. Bracarense, M. Kolf-Clauw, and I. P. Oswald. 2012. Toxicity of deoxynivalenol and its acetylated derivatives on the intestine: Differential effects on morphology, barrier function, tight junction proteins, and mitogen-activated protein kinases. *Toxicological Sciences* 130:180–90.
- Piotrowska, M., K. Sliżewska, A. Nowak, L. Zielonka, Z. Zakowska, M. Gajęcka, and M. Gajęcki. 2014. The effect of experimental fusarium mycotoxicosis on microbiota diversity in porcine ascending colon contents. *Toxins* 6:2064–81.
- Plovier, H., A. Everard, C. Druart, C. Depommier, M. Van Hul, L. Geurts, J. Chilloux, N. Ottman, T. Duparc, L. Lichtenstein, A. Myridakis, N. M. Delzenne, J. Klievink, A. Bhattacharjee, K. C. Van Der Ark, S. Aalvink, L. O. Martinez, M. E. Dumas, D. Maiter, A. Loumaye, M. P. Hermans, J. P. Thissen, C. Belzer, W. M. De Vos, and P. D. Cani. 2017. A purified membrane protein from *Akkermansia muciniphila* or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nature Medicine* 23:107–13.
- Png, C. W., S. K. Linden, K. S. Gilshenan, E. G. Zoetendal, C. S. McSweeney, L. I. Sly, M. A. McGuckin, and T. H. Florin. 2010. Mucolytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria. *The American Journal of Gastroenterology* 105:2420–28.
- Pretzer, G., J. Snel, D. Molenaar, A. Wiersma, P. A. Bron, J. Lambert, W. M. De Vos, R. Van Der Meer, M. A. Smits, and M. Kleerebezem. 2005. Biodiversity-based identification and functional characterization of the mannose-specific adhesin of *Lactobacillus plantarum*. *Journal of Bacteriology* 187:6128–36.
- Puchtler, H., F. S. Waldrop, S. N. Meloan, M. S. Terry, and H. M. Conner. 1970. Methacarn (methanol-Carnoy) fixation - practical and theoretical considerations. *Histochemie* 21:97–116.
- Puel, O., P. Galtier, and I. P. Oswald. 2010. Biosynthesis and toxicological effects of patulin. *Toxins* 2:613–31.
- Rajilić-Stojanović, M. 2013. Function of the microbiota. *Best Practical Research: Clinical Gastroenterology* 27:5–16.
- Rajilić-Stojanović, M., H. G. H. J. Heilig, S. Tims, E. G. Zoetendal, and W. M. De Vos. 2012. Long-term monitoring of the human intestinal microbiota composition. *Environmental Microbiology* 15:1146–59.
- Ranaldi, G., V. Caprini, Y. Sambuy, G. Perozzi, and C. Murgia. 2009. Intracellular zinc stores protect the intestinal epithelium from ochratoxin A toxicity. *Toxicology in Vitro* 23:1516–21.
- Ranaldi, G., E. Mancini, S. Ferruzza, Y. Sambuy, and G. Perozzi. 2007. Effects of red wine on ochratoxin A toxicity in intestinal Caco-2/TC7 cells. *Toxicology in Vitro* 21:204–10.
- Richard, J. L. 2007. Some major mycotoxins and their mycotoxicoses-an overview. *International Journal of Food Microbiology* 119:3–10.
- Riley, R. T., D. M. Hinton, W. J. Chamberlain, C. W. Bacon, E. Wang, A. H. J. Merrill, and K. A. Voss. 1994. Dietary

- fumonisin B1 induces disruption of sphingolipid metabolism in Sprague-Dawley rats: A new mechanism of nephrotoxicity. *The Journal of Nutrition* 124:594–603.
- Robbe, C., C. Capon, B. Coddeville, and J.-C. Michalski. 2004. Structural diversity and specific distribution of O-glycans in normal human mucins along the intestinal tract. *The Biochemical Journal* 384:307–16.
- Round, A. N., N. M. Rigby, A. Garcia De La Torre, A. MacIerzanka, E. N. C. Mills, and A. R. MacKie. 2012. Lamellar structures of MUC2-rich mucin: A potential role in governing the barrier and lubricating functions of intestinal mucus. *Biomacromolecules* 13:3253–61.
- Saint-Cyr, M. J., A. Perrin-Guyomard, P. Houée, J.-G. Rolland, and M. Laurentie. 2013. Evaluation of an oral subchronic exposure of deoxynivalenol on the composition of human gut microbiota in a model of human microbiota-associated rats. *Plos One* 8:e80578.
- Salonen, A., and W. M. De Vos. 2014. Impact of diet on human intestinal microbiota and health. *Annual Review of Food Science and Technology* 5:239–62.
- Sekirov, I., S. L. Russell, L. C. M. Antunes, and B. B. Finlay. 2010. Gut microbiota in health and disease. *Physiological Reviews* 90:859–904.
- Shafquat, A., R. Joice, S. L. Simmons, and C. Huttenhower. 2014. Functional and phylogenetic assembly of microbial communities in the human microbiome. *Trends in Microbiology* 22:261–66.
- Shao, L., O. Kamalu, and L. Mayer. 2005. Non-classical MHC class I molecules on intestinal epithelial cells: Mediators of mucosal crosstalk. *Immunological Reviews* 206:160–76.
- Smith, L. E., A. J. Prendergast, P. C. Turner, M. N. Mbuya, K. Mutasa, G. Kembo, and R. J. Stoltzfus. 2015. The potential role of mycotoxins as a contributor to stunting in the SHINE Trial. *Clinical Infectious Diseases* 61:S733–S737.
- Sokol, H., B. Pigneur, L. Watterlot, O. Lakhdari, L. G. Bermúdez-Humarán, -J.-J. Gratadoux, S. Blugeon, C. Bridonneau, J. P. Furet, G. Corthier, C. Grangette, N. Vasquez, P. Pochart, G. Trugnan, G. Thomas, H. M. Blottière, J. Doré, P. Marteau, P. Seksik, and P. Langella. 2008. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proceedings Natural Academic Sciences USA* 105:16731–36.
- Solcan, C., G. Pavel, V. C. Floristean, I. S. B. Chiriac, B. G. Şlencu, and G. Solcan. 2015. Effect of ochratoxin A on the intestinal mucosa and mucosa-associated lymphoid tissues in broiler chickens. *Acta Veterinaria Hungarica* 63:30–48.
- Sonnenburg, J. L., J. Xu, D. D. Leip, C.-H. Chen, B. P. Westover, J. Weatherford, J. D. Buhler, and J. I. Gordon. 2005. Glycan foraging in vivo by an intestine-adapted bacterial symbiont. *Science* 307:1955–59.
- Streit, E., K. Naehrer, I. Rodrigues, and G. Schatzmayr. 2013. Mycotoxin occurrence in feed and feed raw materials worldwide: Long-term analysis with special focus on Europe and Asia. *Journal of the Science of Food and Agriculture* 93:2892–99.
- Sun, G., S. Wang, X. Hu, J. Su, T. Huang, J. Yu, L. Tang, W. Gao, and J.-S. Wang. 2007. Fumonisin B1 contamination of home-grown corn in high-risk areas for esophageal and liver cancer in China. *Food Additives and Contaminants* 24:181–85.
- Suzuki, T. 2013. Regulation of intestinal epithelial permeability by tight junctions. *Cellular and Molecular Life Sciences* 70:631–59.
- Swanson, S. P., J. Nicoletti, H. D. Rood, W. B. Buck, L. M. Cote, and T. Yoshizawa. 1987. Metabolism of three trichothecene mycotoxins, T-2 toxin, diacetoxyscirpenol and deoxynivalenol, by bovine rumen microorganisms. *Journal of Chromatography* 414:335–42.
- Tailford, L. E., E. H. Crost, D. Kavanaugh, and N. Juge. 2015. Mucin glycan foraging in the human gut microbiome. *Frontiers in Genetics* 5:81.
- Tannous, J., S. P. Snini, R. El Khoury, C. Canlet, P. Pinton, Y. Lippi, I. Alassane-Kpembi, T. Gauthier, A. El Khoury, A. Atoui, T. Zhou, R. Lteif, I. P. Oswald, and O. Puel. 2017. Patulin transformation products and last intermediates in its biosynthetic pathway, E- and Z-ascladiol, are not toxic to human cells. *Archives of Toxicology* 91:2455–2467. doi:10.1007/s00204-016-1900-y.
- Taranu, I., C. Braicu, D. E. Marin, G. C. Pistol, M. Motiu, L. Balacescu, I. Beridan Neagoe, and R. Burlacu. 2015. Exposure to zearalenone mycotoxin alters in vitro porcine intestinal epithelial cells by differential gene expression. *Toxicology Letters* 232:310–25.
- Theumer, M. G., A. G. López, D. T. Masih, S. N. Chulze, and H. R. Rubinstein. 2002. Immunobiological effects of fumonisin B1 in experimental subchronic mycotoxicoses in rats. *Clinical Diagnostics Laboratory Immunology* 9:149–55.
- Thomsson, K. A., J. M. Holmén-Larsson, J. Ångström, M. E. V. Johansson, L. Xia, and G. C. Hansson. 2012. Detailed O-glycomics of the Muc2 mucin from colon of wild-type, core 1- and core 3-transferase-deficient mice highlights differences compared with human MUC2. *Glycobiology* 22:1128–39.
- Tomas, J., J. Reygner, C. Mayeur, R. Ducroc, S. Bouet, C. Bridonneau, J. B. Cavin, M. Thomas, P. Langella, and C. Cherbuy. 2015. Early colonizing *Escherichia coli* elicits remodeling of rat colonic epithelium shifting toward a new homeostatic state. *The ISME Journal* 9:46–58.
- Tomas, J., L. Wrzosek, N. Bouznad, S. Bouet, C. Mayeur, M. L. Noordine, E. Honvo-Houeto, P. Langella, M. Thomas, and C. Cherbuy. 2013. Primocolonization is associated with colonic epithelial maturation during conventionalization. *FASEB Journal* 27:645–55.
- Tsukita, S., M. Furuse, and M. Itoh. 2001. Multifunctional strands in tight junctions. *Nature Reviews. Molecular Cell Biology* 2:285–93.
- Turner, J. R. 2009. Intestinal mucosal barrier function in health and disease. *Nature Reviews Immunology* 9:799–809.
- Van Der Flier, L. G., and H. Clevers. 2009. Stem cells, self-renewal, and differentiation in the intestinal epithelium. *Annual Review of Physiology* 71:241–60.

- Vandenbroucke, V., S. Croubels, A. Martel, E. Verbrugghe, J. Goossens, K. Van Deun, F. Boyen, A. Thompson, N. Shearer, P. De Backer, F. Haesebrouck, and F. Pasmans. 2011. The mycotoxin deoxynivalenol potentiates intestinal inflammation by *Salmonella typhimurium* in porcine ileal loops. *Plos One* 6:e23871.
- Viegas, S., L. Veiga, J. Malta-Vacas, R. Sabino, P. Figueredo, A. Almeida, C. Viegas, and E. Carolino. 2012. Occupational exposure to aflatoxin (AFB₁) in poultry production. *Journal of Toxicology and Environmental Health Part A*. 75(22-23):1330–40.
- Viegas, S., L. Veiga, P. Figueredo, A. Almeida, E. Carolino, R. Sabino, C. Verissimo, and C. Viegas. 2013. Occupational exposure to aflatoxin B1 in swine production and possible contamination sources. *Journal of Toxicology and Environmental Health. Part A* 75:1330–40.
- Von Ossowski, I., J. Reunanen, R. Satokari, S. Vesterlund, M. Kankainen, H. Huhtinen, S. Tynkkynen, S. Salminen, W. M. De Vos, and A. Palva. 2010. Mucosal adhesion properties of the probiotic *Lactobacillus rhamnosus* GG SpaCBA and SpaFED pilin subunits. *Applied and Environmental Microbiology* 76:2049–57.
- Waché, Y. J., C. Valat, G. Postollec, S. Bougeard, C. Burel, I. P. Oswald, and P. Fravallo. 2009. Impact of deoxynivalenol on the intestinal microflora of pigs. *International Journal of Molecular Sciences* 10:1–17.
- Wan, L. Y., P. C. Turner, and H. El-Nezami. 2013a. Individual and combined cytotoxic effects of Fusarium toxins (deoxynivalenol, nivalenol, zearalenone and fumonisins B1) on swine jejunal epithelial cells. *Food and Chemical Toxicology* 57:276–83.
- Wan, L. Y., C. S. Woo, P. C. Turner, J. M. Wan, and H. El-Nezami. 2013b. Individual and combined effects of Fusarium toxins on the mRNA expression of pro-inflammatory cytokines in swine jejunal epithelial cells. *Toxicology Letters* 220:238–46.
- Wan, L.-Y. M., K. J. Allen, P. C. Turner, and H. El-Nezami. 2014. Modulation of mucin mRNA (MUC5AC and MUC5B) expression and protein production and secretion in Caco-2/HT29-MTX co-cultures following exposure to individual and combined Fusarium mycotoxins. *Toxicological Sciences* 139:83–98.
- Wang, E., W. P. Norred, C. W. Bacon, R. T. Riley, and A. H. Merrill. 1991. Inhibition of sphingolipid biosynthesis by fumonisins. Implications for diseases associated with *Fusarium moniliforme*. *The Journal of Biological Chemistry* 266:14486–90.
- Wang, J., L. Tang, T. C. Glenn, and J.-S. Wang. 2016. Aflatoxin B1 induced compositional changes in gut microbial communities of male F344 rats. *Toxicological Sciences* 150:54–63.
- Wang, Z. K., Y. S. Yang, A. T. Stefka, G. Sun, and L. H. Peng. 2014. Review article: Fungal microbiota and digestive diseases. *Alimentary Pharmacology & Therapeutics* 39:751–66.
- Wells, J. M., O. Rossi, M. Meijerink, and P. Van Baarlen. 2011. Epithelial crosstalk at the microbiota-mucosal interface. *Proceedings Natural Academic Sciences USA* 108:4607–14.
- WHO. 1998. *Joint FAO/WHO Expert Committee on Food Additives (JECFA)*. The Hague (The Netherlands): Position paper on patulin, 30th session.
- Wrzosek, L., S. Miquel, M.-L. Noordine, S. Bouet, M. Joncquel Chevalier-Curt, V. Robert, C. Philippe, C. Bridonneau, C. Cherbuy, C. Robbe-Masselot, P. Langella, and M. Thomas. 2013. *Bacteroides thetaiotaomicron* and *Faecalibacterium prausnitzii* influence the production of mucus glycans and the development of goblet cells in the colonic epithelium of a gnotobiotic model rodent. *BMC Biology* 11:61.
- Wu, F., J. D. Groopman, and J. J. Pestka. 2014. Public health impacts of foodborne mycotoxins. *Annual Review of Food Science and Technology* 5:351–72.
- Wu, W., H. R. Zhou, S. J. Bursian, J. E. Link, and J. J. Pestka. 2017. Calcium-sensing receptor and transient receptor Ankyrin-1 mediate emesis induction by deoxynivalenol (vomitoxin). 2017. *Toxicological Sciences* 155:32–42.
- Young, J. C., T. Zhou, H. Yu, H. Zhu, and J. Gong. 2007. Degradation of trichothecene mycotoxins by chicken intestinal microbes. *Food and Chemical Toxicology* 45:136–43.
- Yunus, A. W., K. Ghareeb, A. A. M. Abd-El-Fattah, M. Twaruzek, and J. Böhm. 2011. Gross intestinal adaptations in relation to broiler performance during chronic aflatoxin exposure. *Poultry Science* 90:1683–89.
- Zhang, J., N. Zheng, J. Liu, F. D. Li, S. L. Li, and J. Q. Wang. 2015. Aflatoxin B1 and aflatoxin M1 induced cytotoxicity and DNA damage in differentiated and undifferentiated Caco-2 cells. *Food and Chemical Toxicology* 83:54–60.
- Zhang, S., X. Peng, J. Fang, H. Cui, Z. Zuo, and Z. Chen. 2014. Effects of aflatoxin B1 exposure and sodium selenite supplementation on the histology, cell proliferation, and cell cycle of jejunum in broilers. *Biological Trace Element Research* 160:32–40.
- Zhao, F., R. Li, S. Xiao, H. Diao, M. M. Viveiros, X. Song, and X. Ye. 2013. Postweaning exposure to dietary zearalenone, a mycotoxin, promotes premature onset of puberty and disrupts early pregnancy events in female mice. *Toxicological Sciences* 132:431–42.
- Zhou, H. R., and J. J. Pestka. 2015. Deoxynivalenol (vomitoxin)-induced Cholecystokinin and Glucagon-Like Peptide-1 release in the STC-1 enteroendocrine cell model is mediated by Calcium-sensing receptor and transient receptor potential Ankyrin-1 channel. *Toxicological Sciences* 145:407–17.