

The Gut Immune Parameters for Mycotoxin Research

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Mycotoxins are highly toxic low-molecular-weight secondary fungal metabolites that are produced in response to fungal stress, though not essential to fungal growth [1-3]. They are commonly found on cereals grown in the temperate areas of America, Europe and Asia [4]. Contamination of agricultural crops by fungi and their associated mycotoxins is a serious problem worldwide. In addition to significant economic loss of crops, mycotoxins frequently contaminate food and animal feeds and thus pose a potential health threat to humans and livestock [5]. Following ingestion of contaminated food or feeds, the intestine and the intestinal epithelial cell layer could be exposed to a high concentration of food contaminants, including mycotoxins [6]. The intestinal layer is the first barrier preventing the entry of foreign antigens, including food proteins, natural toxins, commensal gut flora and pathogens, into the underlying tissues through various defense mechanisms (Figure 1). This barrier function is based both on innate and adaptive components of immunity. Mycotoxins investigated in our laboratory affect the intrinsic component of the intestinal immunity, including the epithelial barrier and its inter-cellular junctions (reviewed in, [1]). The trans-epithelial electrical resistance (TEER) of cell monolayer can be considered as a good indicator of the epithelial integrity and of the degree of organization of the tight junctions over the cell monolayer [7] and several studies have demonstrated the reduction in TEER following exposure to mycotoxins (including AFB1, DON and FB1) [8,9]. Such an effect of food toxin on intestinal epithelial cells may increase susceptibility to diseases, possibly due to reduced nutrient retention, combined with greater access of infectious agents. The mechanisms involved in the disturbances of the TEER caused by mycotoxins could be a result of a decrease of two specific isoforms of the claudin protein from the tight junctions [10,11]. Also, effects on the protein content of plasma membrane microdomains, which are known to regulate the tight junction assembly and intestinal transport activity [12] and a loss of cell-matrix interactions [13] may explain the effects of mycotoxins on TEER. In order to maintain an effective barrier function, epithelia need to exist in a constant state of regeneration. Several experiments have also determined the effects of mycotoxins on intestinal cell proliferation and on intestinal morphology. Exposure

to mycotoxins may lead to a reduction in intestinal cell proliferation [14,15], induction of necrosis of epithelial and crypt cells [16] and/or increases in the number of mitotic figures in the intestinal crypts [17]. Mycotoxins have also been reported to affect the extrinsic components of intestinal immunity. While the effects on secretion of immunoglobulin [18-20] and expression of chemokines and cytokines [21-25] have been reported in several studies, their effects on mucus and antimicrobial peptide synthesis and secretion are poorly documented. Recently, our data clearly demonstrated the effects of individual and mixtures of *Fusarium* toxins on endpoints including antimicrobial peptides [26] and pro-inflammatory cytokines [27]. We also demonstrated the involvement of modulation of biosynthesis and secretion of several secretory mucins (MUC5AC and MUC5B) following exposure to different *Fusarium* toxins (not yet published) [28]. Collectively, our preliminary *in vitro* findings demonstrate that ingestion of *Fusarium* toxins may compromise enterocyte-mediated defence responses, which may lead to an increase in the susceptibility of the intestinal mucosa to experimental or natural infections. This warrants further investigation on the effect of mycotoxins on the enterocyte-mediated defence responses in animal models (e.g mice), by looking into different gut immune parameters as summarized in this article (Figure 2). By understanding the effects of mycotoxins on these gut immune parameters, and combining them with tools such as genomics, metabolomics and microbiomics, the results so generated will contribute to improved understanding and risk assessment for common mycotoxins observed in contaminated food and feeds.

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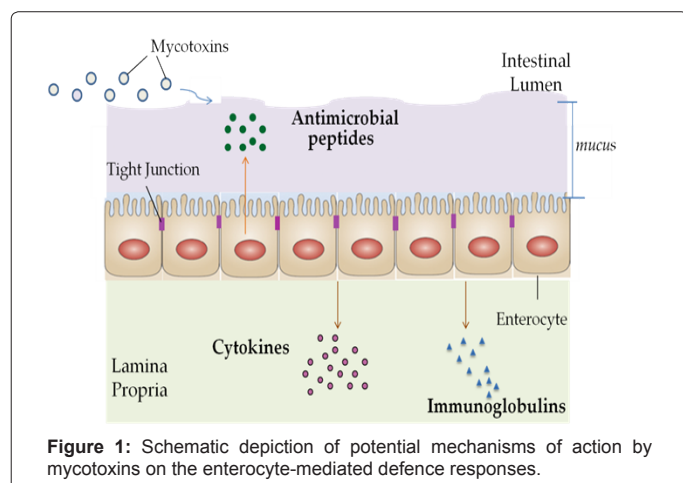


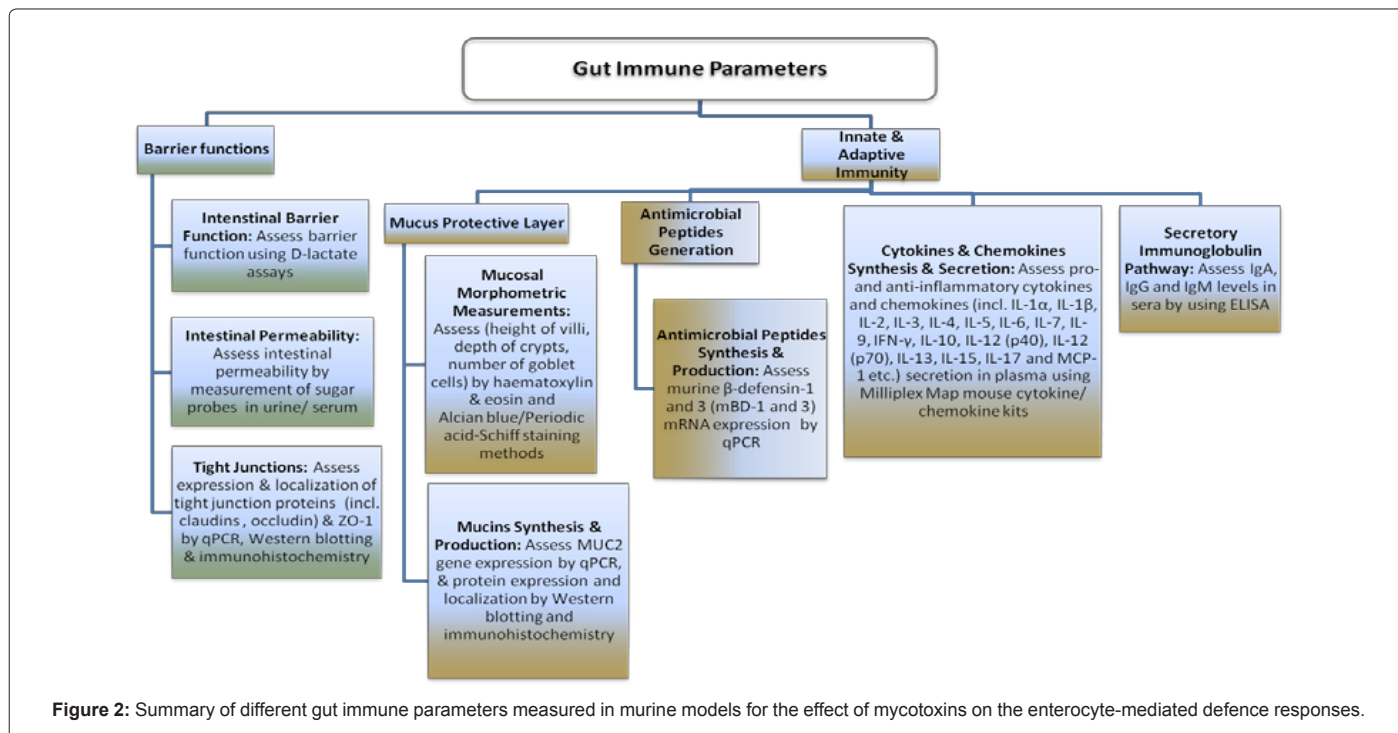
Figure 1: Schematic depiction of potential mechanisms of action by mycotoxins on the enterocyte-mediated defence responses.

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