Biblio_deoxynivalenol_trichothecene_DON_12_04_14

1. Rotter B, Prelusky D, Pestka J. Toxicology of deoxynivalenol (vomitoxin). J Toxicol Environ Health 1996; 48: 1-34.

   Dr. Pestka has written more about DON that anyone I have seen. DON is prevalent in food crops, especially grains. DON can induce a CIRS-like picture in vitro. **NB**: One must ask what difference there is in human host defenses comparing ingested DON versus aerosolized DON?

2. Pestka J, Smolinski A. J Deoxynivalenol: toxicology and potential effects on humans. Toxicol Environ Health B Crit Rev 2005; 8: 39-69.

   DON is far more active in creating illness in animals than in humans. Levels of 1-5 microgram/kg/body weight (1 PPM) are tolerated. This level is massive when considering identification of trichothecenes in urine.

3. Pestka J. Deoxynivalenol: mechanisms of action, human exposure, and toxicological relevance. Arch Toxicol 2010; 84: 663-79.

   Dr. Pestka continues to study this fascinating toxin, finding (as in ochratoxin) a glucuronide in urine (**NB:** one that will likely be detected by ELISA). He feels that DON could be related to growth retardation (data not cited)

4. Pestka J. Deoxynivalenol-induced proinflammatory gene expression: mechanisms and pathological sequelae. Toxins (Basel) 2010; 2: 1300-17.In animals, DON causes robust activation of innate immune mechanisms. Human health effects are far more obscure. (**NB:** Dr. Pestka needs to be involved with our dietary mycotoxin/genomic response trial in humans!).

5. Turner P, Burley V, Rothwell J, White K, Cade J, Wild C. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2008; 25: 864-871. Deoxynivalenol: rationale for development and application of a urinary biomarker.

   A robust urinary assay for trichothecene showed DON frequently in samples and was associated with cereals. Removal of cereals from the diet reduced DON identification.

6. Lancova K, Hajslova J, Poustka J, Krplova A, Zachariasova M, Dostalek P, Sachambula L. Transfer of Fusarium mycotoxins and “masked” deoxynivalenol (deoxynivalenol-3-glucoside) from field barley through malt to beer. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2008; 25: 732-44.

Multiple metabolites of DON and other trichothecenes were identified, as well as the DON glucoside in beer production. (NB: These compounds would likely all give positive ELISA assays in urine.)

7. Kostelanska M, Hajslova J, Zachariasova M, Malachova A, Kalachova K, Poustka J, Fiala J, Scott P, Berthiller F, Krska R. Occurrence of deoxynivalenol and its major conjugate, deoxynivalenol-3-glucoside, in beer and some brewing intermediates. J Agric Food Chem 2009; 57: 3187-94.

   DON-glucoside is a ubiquitous trichothecene found in all 176 types of beer assayed. Maximum levels observed reached 37 micrograms/dl (370 ppb). Stronger beers had more DON metabolites.

8. Latge J. The pathobiology of Aspergillus fumigatus. Trends Microbiol 2001; 9: 382-9.

   No true virulence factor for invasive A. fumigatus has been identified.

9. Chung Y, Jarvis B, Pestka J. Modulation of lipopolysaccharide-induced proinflammatory cytokine production by satratoxins and other macrocyclic trichothecenes in the murine macrophage. J Toxicol Environ Health A 2003; 66: 379-91.

   Low concentrations of trichothecenes superinduce TNF but higher concentrations may suppress such expression.

10. Wu Q, Dohnal V, Kuca K, Yuan Z. Trichothecenes: structure-toxic activity relationships. Curr Drug Metab 2013; 14: 641-60.

    Double bond between C9-C10 and the 12, 13 epoxide ring are essential structural features of the biological effects of trichothecenes. **NB**: Substitutions such as those seen with beta-tubulin-1 associated mutations could increase toxicity.

11. Shank R, Foroud N, Hazendonk P, Eudes F, Blackwell A. Current and future experimental strategies for structural analysis of trichothecenes mycotoxins-A prospectus. Toxins 2011; 3: 1518-1553.

    Terrific paper for chemistry lovers. Very few bacteria are sensitive to trichothecenes but there are significant differences in plant susceptibility to these secondary metabolites. Some probiotics detoxify DON by opening the epoxide ring. (**NB**: those who teach us that mycotoxins are made to kill bacteria need to read this paper. Time to get rid of that assumption.) Trichothecenes are amphipathic which means they can enter a cell by direct translocation (**NB**: this is a variant for the functioning of ionophores). Significant numbers of non-trichothecenes have structures shown by X-Ray crystallography to be ones that look like trichothecenes (**NB:** in ELISA assays).

12. Pepeljnjak S, Slobodnjak Z, Segvic M, Peraica M, Pavlovic M. The ability of fungal isolates from human lung aspergilloma to produce mycotoxins. Hum Exp Toxicol 2004; 23: 15-9.

Production of mycotoxins in vitro does not reflect what fungi do in humans. No Aspergillus isolated from human aspergillomas made aflatoxin or ochratoxin A.

13. Yike I, Rand T, Dearborn D. The role of fungal proteinases in pathophysiology of Stachybotrys chartarum. Mycopathologia 2007; 164: 171-81.

    Proteinases from Stachy contribute to lung injury.

14. Miller J, Sun M, Gilyan A, Roy J, Rand T. Inflammation-associated gene transcription and expression in mouse lungs induced by low molecular weight compounds from fungi from the built environment. Chem Biol Interact 2010; 183: 113-24.

    Exposure to toxins induced inflammatory responses in lung tissue of mice. Transcriptional activation can occur as an antecedent to the inflammatory responses.

15. Rand T, Dipenta J, Robbins C, Miller J. Effects of low molecular weight fungal compounds on inflammatory gene transcription and expression in mouse alveolar macrophages. Chem Biol Interact 2011; 190: 139-47.

    Incredibly convincing studies of inflammation induced by exposure to components of WDB continue to be produced by Dr. Rand and his various collaborators. Transcriptional responses are confirmed to occur following exposure to low molecular weight compounds found in WDB.

16. Rand T, Sun M, Gilyan A, Downey J, Miller J. Dectin-1 and inflammation-association gene transcription and expression in mouse lungs by a toxic (1,3)-beta-D glucan. Arch Toxicol 2012; 84: 205-20.

    Induction of inflammation-gene responses is key for understanding curdlan toxicity. Dectin-1 and dectin-2 effects are related to gene activation.

17. Muller F, Seidler M, Beauvais A. Aspergillus fumigatus biofilms in the clinical setting. Med Mycol 2011; 49 Suppl 1: S96-S100. doi: 10.3109/13693786.2010.502190. Epub 2011.

    Anti-fungals must be able to penetrate biofilms (**NB**: Most azoles really are ineffective attacking biofilms)

18. Singhal D, Baker L, Wormald P, Tan L. Aspergillus fumigatus biofilm on primary human sinonasal epithelial culture. Am J Rhinol Allergy 2011; 25: 219-25.

    In vitro conditions permitted study of surgical specimens of fungal sinusitis. Biofilm formation was noted.

19. Boase S, Jervis-Bardy J, Cleland E, Pant H, Tan L, Wormald P. Bacterial-induced epithelial damage promotes fungal biofilm formation in a sheep model of sinusitis. Int Forum Allergy Rhinol 2013; 3: 341-8.

Fungal biofilm in sinuses only forms if there is pre-existing bacterial biofilm (not including H. influenza). Injury to epithelial defenses by a fungal cilia toxin (not identified) enabled proliferation of fungi. Fungal biofilm did not increase mucosal inflammation. (**NB**: this study is small and was done in sheep.)

20. Seidler M, Salvenmoser S, Muller F. Aspergillus fumigatus forms biofilms with reduced antifungal drug susceptibility on bronchial epithelial cells. Antimicrob Agents Chemother 2008; 52: 4130-6.

    In vitro biofilm growth created resistance to antifungal drugs. **NB**: Again a small in vitro study ignores the dynamics of mucus.

21. Bruns S, Seidler M, Albrecht D. Salvenmoser S, Remme N, Hertweck C, Brakhage A, Kniemeyer O, Muller F. Proteomics 2010; 10: 3097-107. Functional genomic profiling of Aspergillus fumigatus biofilm reveals enhanced production of the mycotoxin gliotoxin.

    In culture and in vitro growth of A. fumigatus can upregulated genes for gliotoxin production.

22. Muller F, Seidler M, Beauvais A. Aspergillus fumigatus biofilms in the clinical setting. Med Mycol 2011; 49 Suppl 1:S96-S100. doi: 10.319109/13693786.2010.502190.

    Aspergillus fumigatus biofilms are described. Penetration of the complex mesh of fungal biofilms is needed to eradicate these organisms in vitro.

23. Waldorf A. Host-parasite relationship in opportunistic mycoses. Crit Rev Microbiol 1986; 13: 133-72.

    Early, but voluminous work. The role of infection with Aspergilli and Mucor are ones in which host defects in immune response must occur. A variety of forms of these organisms are presented with unique antigens for each for which a different host response must occur.

24. Waldorf A. Pulmonary defense mechanisms against opportunistic fungal pathogens. Immunol Ser 1989; 47: 243-71.

    More from Dr. Waldorf. Anti-hyphal defenses are primarily neutrophil-driven, as in ochratoxin-formers. **NB**: Role of T reg cells unknown back then.

25. Sugui J, Kim H, Szrember K, Chang Y, Gallin J, Nierman W, Kwon-Chung K. Genes differentially expressed in conidia and hyphae of Aspergillus fumigatus upon exposure to human neutrophils. PLoS One 2008; 3: e2655. doi: 10.1371/journal.pone.0002655.

    Conidia exposed to neutrophils reprogram their gene activity. No genes involved with toxin production were upregulated. Iron/copper assimilation is upregulated.

26. Zarember K, Sugui J, Chang Y, Kwon-Chung K, Gallin J. J Immunol 2007; 1178: 6367-73.

Reactive oxygen species arrest growth of Aspergilli. Neutrophil sequestration of iron is an important host defense (see paper 25 above).

27. Rose M, Voynow J. Respiratory tract mucin genes and mucin glycoproteins in health and disease. Physiol Rev. 2006; 86: 245-78.

    Mucin is a highly glycosylated macromolecules (NB: > 50% carbohydrate, therefore low a(w)) that provide significant defenses against pathogens and environmental toxins. Comprehensive study.

28. Lillehoj E, Kato K, Lu W, Kim K. Cellular and molecular biology of airway mucins. Int Rev Cell Mol Biol 2013; 303: 139-202.

    Another very long paper. Cellular and molecular properties of mucin are complex and diverse.

29. Voynow J, Rubin B. Mucins, mucus, and sputum. Chest 2009; 135: 505-12.

    Mucus provides important innate immune function by detoxifying noxious molecules. Reduction of intact mucin can predispose to airway disease such as cystic fibrosis

30. Jeffery P, Zhu J. Mucin-producing elements and inflammatory cells. Novartis Found Symp 2002; 248: 51-68.

    Airway goblet cells are the major sources of mucins. Release of inflammatory cell secretions and IL-4, IL-13 contribute to hypersecretion of mucus.

31. Evans C, Koo J. Airway mucus: the good, the bad, the sticky. Pharmacol Ther 2009; 12: 332-48.

    New interventions directed at mucin overproduction will have a role in prevention of illness.

32. Lai H, Rogers D. New pharmacotherapy for airway mucus hypersecretion in asthma and COPD: targeting intracellular signaling pathways. J Aerosol Med Pulm Drug Deliv 2010; 23: 219-31.

    Focus is on inflammatory mediators involved with mucus activity. T reg cell factors such as FOXA2 have key role.

33. Lai H, Rogers D. Mucus hypersecretion in asthma: intracellular signaling pathways as targets for pharmacotherapy. Curr Opin Allergy Clin Immunol 2010; 10: 67-76.

    Similar work as above paper 32.

34. Kondo Y, Yoshimoto T, Tasuda K, Futatsugi-Yumikura S, Morimoto M, Hayashi N, Hoshino T, Fujimoto J, Nakanishi K. Administration of IL-33 induces airway hyperresponsiveness and goblet cell hyperplasia in the lungs in the absence of adaptive immune system. Int Immunol 2008 20: 791-800.

Intriguing paper showing that IL-33 actually does all the bad things we don't want for respiratory health. **NB**: TGF beta-1 can induce IL-33.

35. Ishikawa Y, Yoshimoto T, Nakanishi K. Contribution of IL-18-induced innate T cell activation to airway inflammation with mucus hypersecretion and airway hyperresponsiveness. Int Immunol 2006; 18: 847-55.

The same investigators as in paper 34. Add IL-12 and IL-18 to the list of adverse inflammatory mediators in airway hypersecretion and spasm.

36. Rogers D. Airway goblet cells: responsive and adaptable front-line defenders. Eur Respir J 1994; 7: 1690-1706.

Classic paper looking at goblet cells and illness. NB: The interaction of goblet cells and ciliated cells suggests a role for TGF beta-1 transforming cell types in upper airway respiratory epithelium.

37. Kwon-Chung, Sugui J. What do we know about the role of gliotoxin in the pathobiology of Aspergillus fumigatus? Med Mycol 2009; 47 (Suppl 1): S97-103.

Multiple studies disagree markedly on production of gliotoxin in immunocompromised patients infected with A. fumigatus. No conclusion re gliotoxin formation in tissues can be made. Additional information of geographic variability is needed. Agents that induce activation of the gliotoxin production cluster are not defined.

Key take home messages here are that DON is a ubiquitous trichothecene that can be detected in urine following consumption of foods and fermented beverages. Role of mucins in protection of mucus membranes is tied to innate and cell mediated immunity. Given low a(w) of mucins and goblet cell secretions it is unlikely that endogenous mycotoxin production is a factor in lung, nasal mucosa or sinus.