

Biblio_eosinophils_MBP_EMT_TGF beta__01_14_2015

I have treated patients with eosinophilic esophagitis EE with excellent success simply by lowering TGF beta-1. Granted, none of these cases have presented with profound dysphagia from esophageal stricture. But the success I have seen suggests that reviewing eosinophilic illnesses elsewhere might be a good idea. I am aware of clinical trials using antagonists of IL-5 to treat EE, but who needs them? To date, however, the universe of EE for me is less than 20.

A tantalizing common feature of EE with chronic rhinosinusitis (CRS) is the role of TGF beta-1 involvement as a factor participating in activation of nuclear transcription factors (like the Smads) as an antecedent physiologic factor. TGF beta-1 can be increased in CRS but has other sources as well, particularly Th17-T reg imbalance. It remains fascinating that the role of eosinophils in CRS involves eosinophil-derived neurotoxin; we find it active in EE also. We would be well advised to follow the scant literature of stimulation of eotaxin by TGF beta-1 and conversely, we should be alert for reporting of reduced levels of retinoic acid orphan receptors (ROR) in these tissues as well, as such presence will enhance adverse effects of TGF beta-1 through a Smad3 genomic interaction.

This bibliography is part of a series posted on www.survivingmold looking at claims made by some authors that fungi in nasal cavities make people ill by making mycotoxins. Invariably we see measurement of mycotoxins in urine cited and work from Jens Ponikau's collaborators referenced. This annotated bibliography will show you the problems are far more than just a few benign fungi floating in mucus: we are looking at differential gene activation initiated by eosinophils, mediated by TGF beta-1 that go directly to sources of illness. There is much to be done but measuring mycotoxins and blindly tossing around antifungals is wrongheaded.

Summing, what we know is that benign colonization of upper airways does not result in mycotoxin production; and use of anti-fungals in any form will not affect constant fungal carriage of benign organisms. The data on *what else* is in sinuses that could stimulate eosinophilic infiltration is not clear. All we can say at this point is that the infiltration of eosinophils and the following series of inflammatory compound releases from eosinophils is not confirmed to be caused by presence of fungi. The parallels of EE, eosinophilic gastroenteritis, eosinophilic myositis too and eosinophils infiltrating in sinuses needs genomic study.

1. Jung W, Kang H, Lee H, Park H, Cho S, Min K, Sohn S. Expression levels of eosinophil granule protein mRNAs in induced sputum reflect airway hyper-responsiveness and airflow limitation. *Tohoku J Exp Med* 2014; 233: 49-56.

Eos granule protein is one of the suite of compounds made by eos in tissue. Use of mRNA by RT-PCR is higher in allergy than in controls.

2. Wan D, Zhang X, Liu X, Li G. Protection of montelukast on OVA-induced eosinophilic gastroenteritis via modulating IL-5, eotaxin-1 and MBP expression. *Immunopharmacol Immunotoxicol* 2013; 35: 625-6.

Montelukast attenuates eosinophil major basic protein in jejunum. Montelukast prevents arise in eotaxin-1 and IL-5 in intestinal tissue and blocks increase of major basic protein. **Why hasn't anyone used intra-nasal montelukast for CRS?**

3. Dellon E, Chen X, Miller C, Woosley J, Shaheen N. Diagnostic utility of major basic protein, eotaxin-3, and leukotriene enzyme staining in eosinophilic esophagitis. *Am J Gastroenterol* 2012; 107: 1503-11.

EE patients have lots of MBP and eotaxin. 51 patients and 54 controls with GERD.

4. Matsuwaki Y, Wada K, Moriyama H, Kita H. Human eosinophil innate response to *Alternaria* fungus through protease-activated receptor-2. *Int Arch Allergy Immunol* 2011; 155 Suppl 1: 123-8.

Eos respond to *Alternaria* by releasing granule proteins and killing the fungus. Dysregulation of innate immune mechanisms may be involved in the pathophysiology of human inflammatory diseases. **Wow, what insight!**

5. Liu Q, Dong F. Gfi-1 inhibits the expression of eosinophil major basic protein (MBP) during G-CSF-induced neutrophilic differentiation. *Int J Hematol* 2012; 95: 640-7.

A mutant of Gfi-1 negative cells can augment mRNA for MBP. Downregulation of Gfi-1 during eo development may allow for rapid expression of MBP. **I don't know that TGF beta-1 downregulates Gfi! Oh my, there is robust literature that says Smad3 does just that. So, the nuclear activation/transcription idea is further supported.**

6. Matsuwaki Y, Wada K, White T, Moriyama H, Kita H. *Alternaria* fungus induces the production of GM-CSF, interleukin-6 and interleukin-8 and calcium signaling in

human airway epithelium through protease-activated receptor 2. *Int Arch Allergy Immunol* 2012; 158 Suppl 1: 19-29.

Alternaria is a player releasing proteases that induce cytokine production and airway changes.

7. Roy R, Klein B. Fungal glycan interactions with epithelial cells in allergic airway disease. *Curr Opin Microbiol* 2013; 16: 404-8.

Fungal carbohydrates stimulate inflammatory allergic responses in airways. **Not toxins; not infection but fungal cell wall carbohydrates. Inflammagens!**

8. Cramer R, Zeller S, Glaser A, Vilhelmsson M, Rhyner C. Cross-reactivity among fungal allergens: a clinically relevant phenomenon? *Mycoses* 2009; 52: 99-106.

Cross reactivity of different species of fungi in allergy is real and significant.

9. Inoue Y, Matsuwaki Y, Shin S, Ponikau J, Kita H. Nonpathogenic, environmental fungi induce activation and degranulation of human eosinophils. *J Immunol* 2005; 175: 5439-47.

Alternaria induce activation events in eos. The substance is heat labile and weighs 60 daltons.

10. Matsuwaki Y, Wada K, White T, Benson L, Charlesworth M, Checkel J, Inoue Y, Hotta K, Ponikau J, Lawrence C, Kita H. Recognition of fungal protease activities induces cellular activation and eosinophil-derived neurotoxin release in human eosinophils. *J Immunol* 2009; 183: 6708-16.

Matsuwaki and Ponikau collaborate to further understanding of innate immune events that may play a role in CRS. No more talk about amphotericin B.

11. Yoon J, Ponikau J, Lawrence C, Kita H. Innate antifungal immunity of human eosinophils mediated by a beta 2 integrin, CD11b. *J Immunol* 2008; 181: 2907-15.

More from Ponikau and additional collaborators. Eos show tissue remodeling functions. Where does that come from? [**You bet: TGF beta-1 and EMT.**] The eosinophilic compound, beta integrin CD11b, binds to fungal cell wall beta glucan. But not chitin. Again, carbohydrates are markers for activation, but not from dectin-1 or dectin-2 receptors.

12. Schmid C, Habermann W, Braun H, Gugatschka M, Oriel B, Smietana J, Stammberger H. Released intranasal eosinophilic major basic protein as a diagnostic marker for polypoid chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2010; 143: 386-91.

Toxic eosinophilic MDP are elevated in polypoid CRS compared to similar non-CRS patients.

13. Kephart G, Alexander J, Arora A, Romero Y, Smyrk T, Talley N, Kita H. Marked deposition of Eosinophil-derived neurotoxin in adult patients with eosinophilic esophagitis. *Am J Gastroenterol* 2011; 105: 298-307.

EE has a marked increase of eo-derived neurotoxin that supercedes eo counts in tissue.

14. Cantarini L, Volpi N, Carbotti P, Greco G, Agliano M, Bellisai F, Giannini F, Alessandrini C, Grasso G, Galeazzi M. Eosinophilia-associated muscle disorders: an immunohistological study with tissue localization of major basic protein in distinct Clinicopathological forms. *J Clin Pathol* 2009; 62: 442-7.

Add MBP in muscle to the list of adverse tissue-based effects of eosinophils.

15. Cho J, Doshi A, Rosenthal P, Beppu A, Miller M, Aceves S, Broide D. Smad3-deficient mice have reduced esophageal fibrosis and angiogenesis in a model of egg-induced eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2014, 59: 10-6.

Smad3 deficient mice have far less esophageal remodeling associated with reduced expression of VEGF. Targeting TGF beta-1/Smad3 pathways may reduce esophageal fibrosis seen in EE.

16. Rochester C, Ackerman S, Zheng T, Elias J. Eosinophil-fibroblast interactions. Granule major basic protein interacts with IL-1 and transforming growth factor-beta in the stimulation of lung fibroblast IL-6-type cytokine production. *J Immunol* 1996; 156: 4449-56.

MBP interacts with fibroblasts. TGF beta-1 stimulates many IL-6-type cytokines. MBP acts synergistically with TGF beta-1 to increase IL-6 production. MBP regulation of cytokine production may play an important role in pathogenesis of eosinophilic disorders or airways and other organs.

17. Cheng E, Souza R, Spechler S. Tissue remodeling in eosinophilic esophagitis. *Am J Physiol Gastrointest Liver Physiol* 2012; 303: G1175-87.

EE is associated with tissue remodeling with increased TGF beta-1 expression.

18. Aceves S, Remodeling and fibrosis in chronic eosinophil inflammation. *Dig Dis* 2014; 32: 15-21.

Remodeling and fibrosis is common in EE. EE is associated with inflammatory changes, including especially TGF beta-1. Tissue remodeling is the key to this illness.

What do we know about tissue remodeling in CRS?

19. Virchow J. Eosinophilic esophagitis: asthma of the esophagus? *Dig Dis* 2014; 32: 54-60.

The similar effects of eosinophils and TGF beta-1 in many tissues is striking.

20. Muir A, Lim D, Benitez A, Modayur Chandramouleeswaran P, Lee A, Ruchell E, Spergel J, Wang M. Esophageal epithelial and mesenchymal cross-talk leads to features of epithelial to mesenchymal transition in vitro. *Exp Cell Res* 2013; 319: 850-9.

TGF beta-1 and remodeling has a mechanism that is seen in lung, liver, kidney, skin and ... sinuses?

21. Kagalwalla A, Akhtar N, Woodruff S, Rea B, Masterson J, Mukkada V, Parashette K, Du J, Fillon S, Protheroe C, Lee J, Amsden K, Melin-Aldana H, Capocelli K, Furuta G, Ackerman S. Eosinophilic esophagitis: epithelial mesenchymal transition contributes to esophageal remodeling and reverses with treatment. *J Allergy Clin Immunol* 2012; 129: 1387-1396.

EMT is the reason for fibrosis in EE.

22. Steinestel K, Eder S, Schrader A, Steinestel J. Clinical significance of epithelial-mesenchymal transition. *Clin Trans Med* 2014; 2: 3-17.

The translational basis of EMT has direct extension to cancer-based molecular events. MicroRNAs have a role in this expanding field. **What do we know about those microRNAs in CRS?**