Using Voluntary Cough Characteristics To Detect Obstructive Lung Disease

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Following standard pulmonary function testing at the West Virginia University Pulmonary Function Laboratory, volunteer patients were classified by physicians as either normal (men = 27; women = 25) or having obstructive lung disease (men= 27; women = 21). Three voluntary coughs were recorded for each subject using the system and procedure previously described (Goldsmith et al., Proc. 3rd Int. W. of Biosig. Interp.). A series of cough sound pressure wave and airflow analyses were conducted for each cough. The sound pressure wave analyses included the cough sound index (Goldsmith et al. Am J Respir Crit Care Med 157:A86 1998), octave filter analysis, determination of β in a 1/f β power spectral analysis and wavelet decomposition. Airflow signal analysis included measurements of peak flow, average flow, mean transient time, β in a 1/f β power spectral analysis, and flow pattern shape indices. A principal component analysis of all the data was performed. The 5 most significant components were selected as inputs to a quasi-Newton back-propagation neural network classification system. The neural network was trained with approximately half the subjects, then the remaining subjects were classified based on that training set. Results were used to construct ROC curves for men and women to compare the results of the cough analysis with the physicians' interpretation of their pulmonary function measurements. The sensitivity and specificity of the cough analysis method for men were equal at 0.93, and the area under the ROC curve, or test discrimination, was 0.97. For women, the sensitivity and specificity were equal at 0.72 and the test discrimination was 0.76. Results indicate that an accurate and rapid classification of patients with obstructive lung disease can be achieved using voluntary cough analysis.

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Effect of Surfactant on Airway Opening: A Thermodynamic Model

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The lung surfactant is an organic mixture of lipids and proteins produced by lung cells that reduces the surface tension of the liquid layer (LL). Lipids are molecules with an amphiphilic character, part of the molecule is hydrophobic and another part is hydrophilic. The formation of a liquid bridge, or airway closure, is driven by capillarity mechanisms, affected by the volume and surface tension of the LL, temperature, and the compliance and geometry of the airway. A capillary liquid always tends to minimize its surface area, where the stable configuration of the systems corresponds to a local minimum of the free energy. In this study, we model the liquid bridge in an airway as an equilibrium thermodynamic system, composed by air, water, surfactant and airway wall. A surfactant molecule is modeled as an amphiphilic dipole. We simulate this model using the Monte Carlo method and interpret the transition between open and collapsed states of the airway as a topological first order transition. These results also suggest that the gap in energy between the the two energy minima (collapsed and open) is the acoustic energy released in the form of a crackle sound during the process of airway opening. We find this energy as a function of surfactant properties, volume of the LL, and size of the airway.

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Upregulation of Toll-Like Receptor 4 by Respiratory Syncytial Virus Sensitizes Airway Epithelial Cells to Endotoxin

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Airway epithelial cells are unresponsive to endotoxin (LPS) exposure under normal conditions. This study demonstrates that respiratory syncytial virus (RSV) infection results in increased sensitivity to this environmental exposure. Infection with RSV results in increased expression of Toll-like receptor (TLR) 4 mRNA, protein, and increased TLR4 membrane localization. This permits significantly enhanced LPS binding to the epithelial monolayer that is blocked by disruption of the golgi. The increased TLR4 results in an LPS-induced inflammatory response as demonstrated by increased MAP kinase activity, IL-8 production and TNF production. RSV infection also allowed for TNF production subsequent to TLR4 cross-linking with an immobilized antibody. These data suggest that RSV infection sensitizes airway epithelium to a subsequent environmental exposure (LPS) by altered expression and membrane localization of TLR4. The increased interaction between airway epithelial cells and LPS has the potential to profoundly alter airway inflammation.

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The Role of Toll Receptor 4 (TLR4) in a Cockroach Allergen (CRA)-Induced Model of Allergic Asthma

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Clinical data has shown that airborne endotoxin can exacerbate existing asthma and that exposure to high levels of endotoxin may offer protection to the development of allergic disorders. The biologic responses to bacterial lipopolysaccharide (LPS), an endotoxin component, are mediated by the TLR4. We sought to delineate the role of LPS in a model of CRA-induced asthma using mice with a defective, non-signaling TLR4. In Protocol 1 either naïve BALB/c mice (WT) or TLR4-defective (TLR4-d) mice were periodically administered intranasal CRA over a 2 week period. Twenty-four hours following last CRA dose, bronchoalveolar lavage was performed and draining lung lymph nodes (DLLN) were harvested. Bronchoalveolar lavage fluid (BALF) inflammatory cell differential was determined and in vitro DLLN CRA-induced IL-13 production was assessed. In order to assess the recall response to CRA in this model, additional cohorts of WT and TLR4-d were treated as above and allowed to rest for 2 weeks and then re-challenged with CRA for 2 weeks (Protocol 2). As shown in the table below, Protocol 1 treatment TLR4-d mice had nearly 3-fold

	2 weeks CRA (Protocol 1)			2 weeks CRA re-challenge (Protocol 2)		
Group	BALF EOS (%)	IL-13 (pg/ml)	IgE (ng/ml)	BALF EOS (%)	IL-13 (pg/ml)	IgE (ng/ml)
WT BALB/c	64±3	2617	507±78	75±3	1348	8105±1335
TLR4-d	24±4*	399	185±16*	72±5*	717	1364±280*

*p<0.05 vs WT BALB/c

fewer BALF eosinophils (EOS), 7-fold and 3-fold lower IL-13 and serum IgE levels, respectively. On CRA re-challenge in Protocol 2 BALF EOS normalized between WT and TLR4-d mice whereas IL-13 production and total serum IgE remained reduced in the TLR4-d mice compared to WT mice.

These data suggest that defective TLR4 signaling in a CRA model of asthma suppresses IgE and IL-13 production and delays the acquisition of a fulminate pulmonary eosinophilia.

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Toll like Receptor Ligands Can Activate Transforming Growth Factor β Via an αvβ6 Integrin Dependent Pathway

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Viral and bacterial infections are implicated in the pathogenesis of a diverse group of fibrotic lung diseases including pulmonary fibrosis, COPD and cystic fibrosis. Activation of transforming growth factor β (TGFβ) is a key step in tissue fibrogenesis, and the αvβ6 integrin regulates this process within the lung. Toll like receptors (TLR's) have a vital role in microbial recognition and represent the first step in the innate immune response. We therefore sought to investigate whether TLR ligands could activate TGFβ via the αvβ6 integrin. We stimulated murine alveolar type 2 cells and normal human bronchial epithelial cells (NHBE) with a TLR3 ligand, poly I:C , and a TLR 5 ligand, flagellin. Cells were stimulated in co-culture with transformed mink lung cells containing a TGFβ responsive promoter driving the luciferase gene. There was a dose dependent increase in αvβ6 dependent TGFβ activation following stimulation of murine alveolar cells with poly I:C (11.9±0.9 RLU, 15.0±1.3 RLU, 16.9±0.8RLU; 0μg/ml, 10μg/ml, 50μg/ml respectively), however flagellin had no effect. In contrast there was a dose dependent increase in αvβ6 dependent TGFβ activation following flagellin stimulation of NHBE cells (0.39±0.1 RLU, 0.72±0.1 RLU, 1.04±0.1; RLU 0ng/ml, 50ng/ml, 100ng/ml respectively) but no response to poly I:C. Because many of the effects of TLR ligation are mediated by p38 MAP kinase, we also sought to determine whether this pathway mediates TLR-induced αvβ6 mediated TGFβ activation. In both cell types αvβ6 mediated TGFβ activation was abrogated by the p38 MAP kinase inhibitors SB202190 and SB203580. These results demonstrate that TLR ligands can lead to αvβ6 mediated TGFβ activation and that these effects may be mediated by p38 MAP kinase pathway. These effects are cell type specific, which suggests a mechanism by which distinct pathogens can promote fibrosis in distinct regions of the lung.

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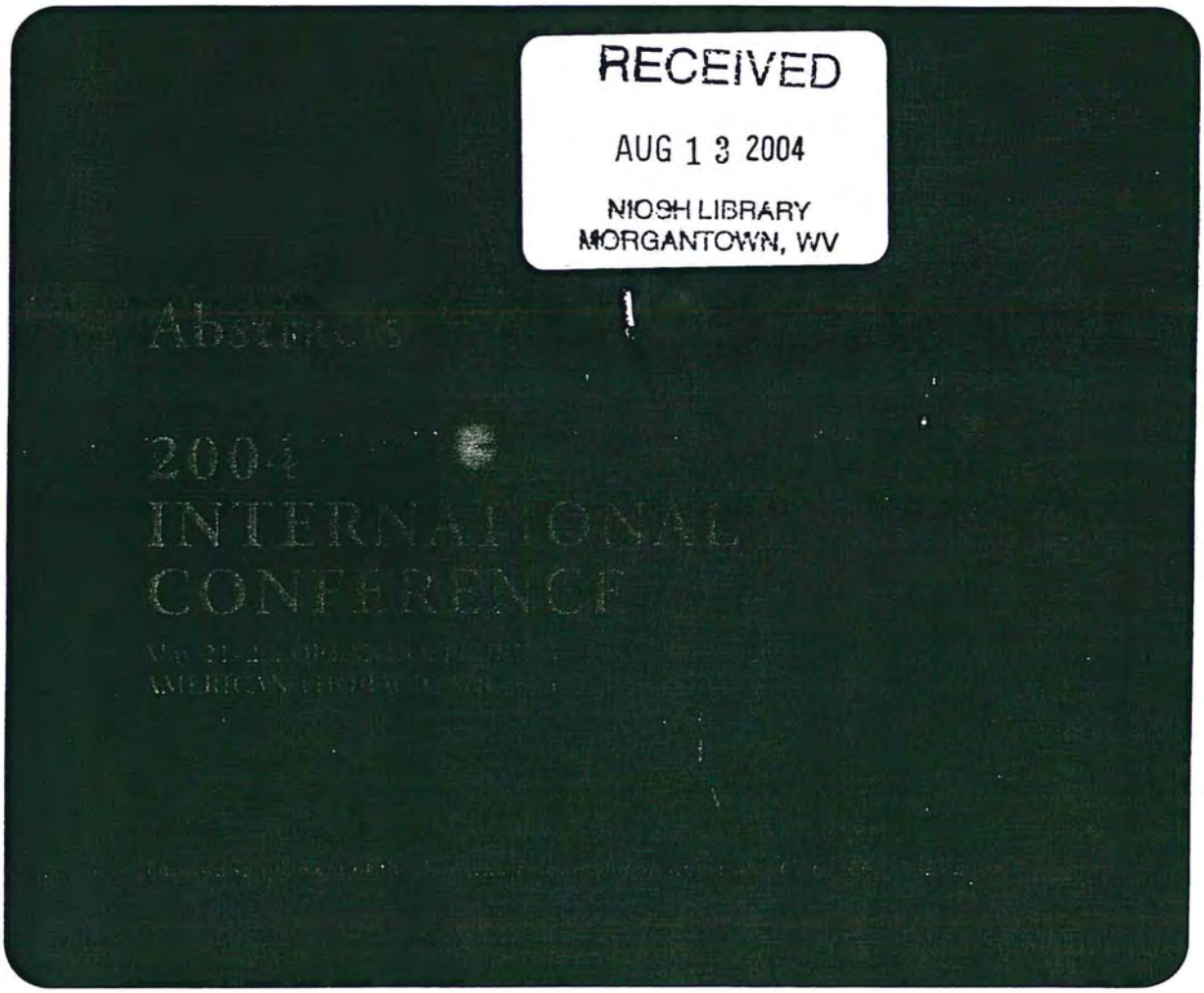

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