New Isocyanate Antigens for Diagnostic Assays

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Hexamethylene diisocyanate (HDI) and other isocyanates are widely used chemicals and a common cause of occupational asthma. Unfortunately, reliable diagnostic tests for isocyanate sensitivity are lacking, and unlike common atopic asthma, RAST/skin prick tests based on specific antigens are frequently negative in isocyanate asthmatics. The apparent lack of isocyanate-specific antibody in sensitized patients may be partly due to the use in diagnostic assays of isocyanate antigens that do not accurately mimic those which occur naturally *in vivo*. We have developed a novel system for generating isocyanate antigens under physiologic conditions, whereby albumin in liquid solution is exposed to vapors of HDI, resulting in HDI-albumin conjugates. These novel vapor/liquid HDI-albumin conjugates perform better in antibody binding assays than those prepared by traditional liquid/liquid phase exposure. Using the vapor/liquid conjugates as antigens: 1) HDI-specific IgE was detected in 6/10 HDI asthmatics tested, compared with 2/10 using liquid/liquid phase exposed antigens, 2) HDI-specific IgG titers were significantly ($p < .001$) associated with exposure in 203 subjects, with fewer false positives than assays performed with liquid/liquid phase exposed antigens. The novel HDI-albumin conjugates are very lightly substituted with HDI (~2-3 mol HDI/albumin) compared with those prepared by liquid/liquid phase exposure [illegible] / sites for HDI conjugation. In [illegible]erate isocyanate antigens under [illegible]prove immunologic assays for [illegible]itization or disease.

Exhaled Nitric Oxide Measurement in Microwave Popcorn Production Plant Workers

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RATIONALE: Two former microwave popcorn production plant workers had pathology consistent with bronchiolitis obliterans. The prevalence of respiratory problems and airways obstruction among current workers were higher than expected. Exhaled nitric oxide (ENO) was measured in workers at risk for developing lung disease. METHODS: One hundred thirty five workers completed a questionnaire, spirometry and ENO measurement. Workers with relatively high exposures (n=107, mixing, microwave packaging, maintenance, and quality control) were compared to workers with low exposure from other areas of the plant (n= 28). RESULTS: ENO was lower in the 135 current workers (median 5.9 ppb) when compared to an external control group of 31 healthy never smokers (median 7.6 ppb) (p=0.001). ENO was lower in the high-risk group of workers (median 5.5 ppb) when compared to the low risk group (median 6.6 ppb) (p=0.03). There were no significant associations between ENO and current respiratory symptoms or lung function. However, after adjusting for smoking status, workers with current systemic symptoms were more likely than other workers to have a high ENO [chills OR: 7.8 (95% CI: 1.1-58.3); night sweats OR: 8.3 (95% CI: 1.1-64.6); fever OR: 4.0 (95% CI: 0.9-18.3)]. CONCLUSION: In this study of microwave popcorn workers, ENO was not useful for distinguishing between groups of workers with and without respiratory symptoms or lung function abnormalities. However, the association of ENO with systemic symptoms suggests that ENO might be useful in the study of inhalation fever or other inhalation syndromes.

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Hot Tub Associated Granulomatous Lung Disease from Mycobacterial Bioaerosols

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Rationale: The spectrum of diseases from nontuberculous mycobacteria (NTM) is expanding, and the incidence of NTM pulmonary disease in immunocompetent hosts is increasing. We describe the clinical, functional, and radiologic features of a series of 27 patients with granulomatous pneumonitis from exposure to hot tub and therapy pool bioaerosols. Methods: We reviewed charts of all patients seen in our clinic from 1994-2002 for hypersensitivy pneumonitis (HP, ICD9 code 495.1-495.9). We included all patients whose HP was attributed to a hot tub or therapy pool. Results: Median latency between exposure to symptom onset was 10 months (range 2 months to 11 years). Cases reported symptoms of dyspnea (100%), fatigue (85%), cough (78%), fever/chills (59%), and wheezing (52%) . Reduced DLCO occurred in 54%. Only 9 of 27 patients had initially normal resting pulmonary function. HRCT findings included centrilobular nodules (81%), ground glass (58%), and air-trapping (50%). NTM were cultured from sputum or BAL in 17 (65%). Twelve cases were treated with antibiotics plus steroids, 13 with steroids alone, and 2 with expsoure removal only. Significant improvement or disease resolution occurred in all. Air and water cultures of implicated hot tubs and pools in 11 patients showed a mean NTM water concentration of 115,585 cfu/ml (range: 32-600,000) and a mean air concentration of 3643 cfu/M^3 (range: 15-9,424). Conclusions: Exposure to NTM aerosols from contaminated pools and spas may cause a granulomatous lung disease with features of HP. Early recognition and management leads to a favorable prognosis.

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Smad 3 KO Mice Are Resistant to TGF-β1 Mediated Fibrogenesis and I Induce a Pro-Fibrotic Microenvironment

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TGF-β1 is one of the key cytokines involved in the pathogenesis of pulr fibrosis. Smads are a family of signal transducer proteins with Smad3 me directly signaling from activated TGF-β1 receptor type I. Smad3 deficiency atte bleomycin induced lung fibrosis in mice (Zhao et al). We assessed fibrosis de ment and fibrotic gene responses in smad3 null mice after direct transient TGF-β expression in lung.

Adenovirus encoding for active TGF-β1 (AdTGF-β1) was administered (intra-nasally to smad3 KO or WT mice. Fibrosis extent was evaluated at day 28 (e group). Total lung RNA from treated mice 4 days after vector instillation (4 to 5/ was analysed by quantitative RT-PCR analysis for known TGF-β related gene expr

At day 28 after AdTGF-β1, lungs showed large amounts of fibrotic tissue, con by histology with trichrome masson and picrosirius red staining in WT mice. evidence of fibrosis was observed in KO mice. This difference was confirm hydroxyproline assay. By day 4 after AdTGF-β1, WT mice showed an expected s icant increase in matrix components (procollagen3a1, CTGF), antiproteases (T TIMP-1) and αSMA mRNA expression. There was no difference between WT ar mice before treatment and no significant increased expression of these genes i mice at day 4 after adenoviral exposure. These data were confirmed in primary fibroblast lines exposed to rTGF-β1 (1ng/ml).

Conclusion: Blocking TGF-β1 responses by targeting Smad3 inhibits the pr tion of the necessary microenvironment leading to fibrosis.

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Complement Receptor 1 Gene Polymorphisms in Idiopathic Pulmonary Fibr

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Erythrocyte (E) complement receptor 1 (CR1) is a membrane protein mediatin transport of immune complexes (ICs) to phagocytes. Three polymorphic sites o CR1 gene (His1208Arg, intron 27 HindIII RFLP, and Pro1827Arg) are related surface density of CR1, in turn related to the rate of IC clearance. We previo demonstrated an association between sarcoidosis and CR1 genotypes coding reduced CR1/E ratio (Zorzetto et al AJRCMB 2002;27:17). Since Idiopathic Pul nary Fibrosis (IPF) shares with sarcoidosis the hypothesis of putative triggering e enous factor(s), we hypothesized that a late clearance of ICs might be involved in pathogenesis of IPF too. To this aim we analyzed the 3 CR1 polymorphisms by P RFLP and direct sequencing in a group of 73 patients affected by IPF, as well as in sex-, age-, and ethnicity-matched controls. We first had evidence that the intron HindIII RFLP is a T-to-C substitution nt 520 (GeneBank access number AY 1585 The 3 polymorphisms were in strong linkage disequilibrium. The GG genotype for Pro1827Arg (C5507G) polymorphism, related to an E surface low density of CR1 m cules, was significantly associated with IPF in comparison to controls ($X2 = 8.74$ OR= 6.86, 95% CI 2.00 - 14.93). These findings are consistent with a novel, possi susceptibility gene factor for IPF. Morover, it opens to intriguing speculations abo susceptibility factor shared by two interstitial lung disease, sarcoidosis and IPF.

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Augmented Pulmonary IL-4 and IL-13 Receptor Subunit Expression in Id pathic Interstitial Pneumonia

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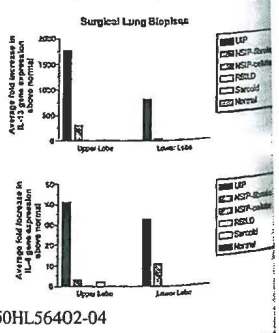
Some idiopathic interstitial pneumonias (IIP) are characterized by fibro-proliferati Since efficacious treatments are limited, research has been directed towards understandi the cytokine networks associated with IIPs. In the present study, we hypothesized th severe IIP is dominated by interleukin-4 (IL-4) and IL-13 due to the abnormal expression their corresponding receptor subunits. [figure1] Molecular, protein, and biochemical ana ysis of surgical lung biopsies (SLB) from patients suspected of having IIP (n=45) demo strated that IL-4 and IL-13 were present in higher levels in biopsies from patients with hist logically confirmed usual interstitial pneumonia (UIP; n=18) and non-specific interstitial pneumonia-fibrotic form (NSIP-fibrotic; n=7) compared with patients with lesser aggressive forms of IIP (n=8) and non-IIP (n=12) controls. Immunohistochemical analysis revealed that fibroblastic foci in UIP and NSIP-fibrotic patients strongly stained for the presence of the IL-4 receptor alpha (IL-4Rα) and IL-13Rα2. Thus, this study demonstrates that some histologic subtypes of IIP are associated with increased pulmonary expression of receptor subunits responsive to IL-4 and IL-13. These findings may be of particular importance in describing the pathogenesis of IIPs and, more importantly, may provide important novel therapeutic targets.



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