epithelial cells, but is also present on airway ciliated epithelial cells and smooth muscle cells. The staining pattern was most pronounced on the plasma membranes of these cells. Preliminary functional studies demonstrated that the estrogen receptor agonist 17β-estradiol relaxed airway rings contracted by acetylcholine. The effects of 17β-estradiol were reversed by tamoxifen.

CONCLUSION: This is the first demonstration of the presence of ER-α36 on lung tissue. The increased expression in allergen-sensitized mice suggests a possible role of this novel receptor in estrogen-related asthma effects.

Funding: Creighton University

1175 Airway Fibroblasts Isolated from Mouse Model of Allergic Asthma Display Distinct Cellular and Phenotypic Characteristics as Compared to Normal Fibroblasts

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RATIONALE: Airway remodeling is considered a major hallmark of asthma, but a clear understanding of the mechanisms underlining this phenomenon is lacking. We therefore investigated if acquired functional and phenotypic changes in airway fibroblasts could contribute to the development of airway remodeling using a murine model of asthma.

METHODS: The mouse model of asthma was established by sensitizing and challenging female BALB/c mice with ovalbumin. DNA microarray experiments were performed to determine differential gene expression. In vitro release of TGF-β1, VEGF, and fibronectin was measured by ELISA. Collagen gel contraction assays were performed to simulate the effect of fibroblasts on actin contraction. α-SMA expression was measured by Western blot. Fibroblast cell migration ability was assessed by using Boyden chamber. Finally, fibroblast proliferation rate was determined.

RESULTS: Many genes were differentially expressed when fibroblasts from "asthmatic" versus control mice were compared. Airway fibroblasts from asthmatic mice displayed significant increase in collagen gel contraction ability, chemotactic activity, α-SMA expression, and growth factors (TGF-β1, VEGF, fibronectin) release in comparison to control mice. Moreover, fibroblasts from asthmatic mice proliferated at more than twice the doubling rate of fibroblasts from control mice.

CONCLUSIONS: These results revealed that, at least in an animal model of asthma, asthmatic fibroblasts acquire a distinct phenotype that differs from control fibroblasts. The increased pro-fibrotic activity and mediator release by asthmatic fibroblasts suggest that these cells could play an important role in the development of airway remodeling in asthma.

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1176 Effect Of Cetirizine On Early- And Late-phase Airway Responses In A Brown Norway Rat Model Of Allergic Asthma

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RATIONALE: The effect of Cetirizine, a selective H1-receptor antagonist, was studied in the Brown Norway rat (BNR) model of trimellitic anhydride (TMA) early and late phase allergic asthma.

METHODS: Rats were sensitized by 4 hr, weekly applications of 40 mg dry TMA powder on the rats' dorsum for 4 weeks. Two weeks after the final exposure, BNR were challenged with a 10 min, 40 mg/m^3 TMA aerosol inhalation exposure and enhanced pause (Penh, an index of airway resistance) was recorded continuously overnight. Cetirizine (15 or 30 mg/kg, i.p.) was given 30 min before or 1 hr after TMA challenge.

RESULTS: Both doses of Cetirizine when administered 1 hr after TMA challenge attenuated the late-phase airway response (LAR). Thirty mg/kg Cetirizine administered prior to airway challenge did not inhibit the early-phase airway response (EAR), but again the late-phase airway response was inhibited.

CONCLUSIONS: The data suggest that the H-1 histamine receptor does not play a major role in the EAR, but is involved in LAR physiological response in the BNR TMA allergic asthma model.

Funding: NIOSH/CDC

1177 Nor-nordihydroguaiaretic Acid (NDHGA) Ameliorates C5a-Induced Acute Peritonitis

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RATIONALE: We have investigated the effect of nordihydroguaiaretic acid (NDHGA) in the anaphylatoxin C5a-triggered responses in vivo.

METHODS: The C5a-intraperitoneal (i.p.) injection triggered a fast recruitment of neutrophils followed by monocytes into the peritoneal cavity in mice. Extravasation due to the vascular permeability was also observed: when we i.v. injected Evans blue before C5a i.p. injection, we could observe a continued influx of the dye into the peritoneum.

RESULTS: Our data show that i.v. administration of C5a triggers a rapid reduction in neutrophil level but pre-treating mice with the NDHGA 10 min before the C5a i.v. administration substantially inhibited the C5a-triggered neutropenia. Similarly the i.v. administration of C5a caused a rapid increase in the serum levels of IL-6 and TNF-α and, and this increase in cytokine levels was blocked by NDHGA. In mice pretreated with NDHGA, there was a significant reduction on the C5a-triggered neutrophil and monocyte infiltration, as well as a marked reduction on the Evans blue influx. In addition, the i.p. administration of C5a caused a rapid elevation in IL6 and TNF α level in the peritoneal cavity, and this elevation in cytokine levels was significantly inhibited in mice pretreated with NDHGA.

CONCLUSIONS: Taken together, these observations suggest that NDHGA treatment potentially blocks the C5a-triggered inflammatory responses in vivo.

Funding: National University of Singapore

1178 Biochemical Efficacy and Tolerability of a New Augmentation Preparation in Two Patients with $M_{MALTON}Z$ Alpha1-Antitrypsin Deficiency

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RATIONALE: One function of alpha$_1$-antitrypsin (AAT) is to inhibit neutrophil elastase, a serine proteinase released from neutrophils in the lower airways and lung parenchyma. If serum AAT is deficient as a result of genetic determinants, elastin degradation with pulmonary emphysema may ensue. Disease risk and management of individuals with the PiZ phenotype is well characterized. Comparatively little is known about the management of patients with the rare M_{Malton} (PiM_{Malton} and PiM_{Malton}Z) phenotype of AAT deficiency.

METHODS: Two patients with $M_{Malton}Z$ phenotype were included in open-label clinical studies of Zemaira® (ZLB Behring) [Z(A_1-PI)] intravenous augmentation therapy. One patient underwent bronchoalveolar lavage (BAL) to assess A_1-PI levels in the epithelial lining fluid (ELF) of the lung.

RESULTS: Patient *A* received a single intravenous infusion of Z(A_1-PI) 120 mg/kg. Patient *B* was included in 2 separate trials of Z(A_1-PI), receiving a single infusion of 30 mg/kg in one, and weekly infusions of 60 mg/kg for 6 months in the other. Z(A_1-PI) was well tolerated.

Patient *A*: Plasma antigenic A_1-PI levels before and after infusion were 4.99 μM and 71 μM (max). BAL assessment showed that A_1-PI levels reached the ELF in concentrations similar to PiZZ recipients.

Patient *B*: Plasma antigenic A_1-PI levels before and after a single infusion were 6.78 and 23.80 μM, and remained above 11 μM throughout the separate 6-month study.

CONCLUSIONS: Z(A_1-PI) has been evaluated in patients with the common PiZZ variant (COPD 2006;3:17-23). These results suggest patients with $M_{Malton}Z$ phenotype can also be treated with Z(A_1-PI).

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