Three variants in the 5p15.33 locus encompassing the TERT and CLPTM1L genes investigate whether the lung cancer susceptibility locus on chromosome 5p15.33 increases susceptibility to lung cancer. We assess the possibility of a common genetic origin and investigate whether the lung cancer susceptibility locus on chromosome 5p15.33 increases the risk for bronchial obstruction and emphysema.

Clinical studies suggest that bronchial obstruction and emphysema increase susceptibility to lung cancer. We assess the possibility of a common genetic origin and investigate whether the lung cancer susceptibility locus on chromosome 5p15.33 increases the risk for bronchial obstruction and emphysema.

Three variants in the 5p15.33 locus encompassing the TERT and CLPTM1L genes were genotyped in 777 heavy smokers and 212 lung cancer patients. Participants underwent pulmonary function tests and computed tomography (CT) of the chest, and took questionnaires assessing smoking behaviour.

The rs31489 C-allele correlated with reduced forced expiratory volume in 1 second (FEV1) (β=0.006). Homozygous carriers of the rs31489 C-allele exhibited increased susceptibility to bronchial obstruction with an odds ratio (OR) of 1.82 (95% confidence interval [CI]=1.94-2.69; P=0.002). A similar association was noticed for lung diffusing capacity (DLCO; P=0.004). Consistent herewith, CC-carriers had increased risk of emphysema (OR=2.04; CI=1.41-2.94; P=0.73×10^-4) and displayed more alveolar destruction. Finally, CC-carriers had also increased risk for lung cancer (OR=1.10; CI=1.21-2.99; P=0.005) and were more susceptible to develop both lung cancer and bronchial obstruction than lung cancer alone (OR=2.11; CI=1.04-4.26; P=0.038). The rs31489 variant on 5p15.33 is associated with bronchial obstruction, the presence and severity of emphysema and lung cancer.

**Methods:**

To compare 25OHD levels in controlled and uncontrolled asthmatic children and healthy controls; to genotype, in asthmatics, 2 SNP in the VDR gene.

**Aims:**

To investigate whether the TNF-derviep SNP, which reduces PLY-induced edema, can blunt IAV-induced ALC dysfunction and combined IAV/PLY-induced barrier dysfunction.

**Results:**

IAV infection reduces basal ALC by 50±6%, which is prevented by co-administration of the Tert SNP (2.5 mg/kg; n=11). The combination of PLY (7.5 ng/ml) and UV-inactivated IAV (1 virus/cell) causes a significant drop in normalized TER in HL-MVEC monolayers from 100 to 40±8% of baseline. The Tert SNP (50 µg/ml), as well as Ro32-4032 (10 µM), a specific inhibitor of PKC-α, implicated in both ALC dysfunction and hyperpermeability, restore TER to 86±4% and 80±6% of ctrl, respectively (n=4). IAV-treatment increases PCK-α activation by 110±7% over basal in HL-MVEC, an effect significantly blunted by the Tert SNP (23±1% over basal, n=4).

**Conclusions:**

The Tert SNP represents a therapeutic candidate for the treatment of IAV-associated lung dysfunction, since it interferes with both IAV infection-associated ALC and barrier dysfunction, upon reducing PKC-α activation.

**Oxidative stress during high altitude expedition and its influence on vessel tone-modifying mediators**

Jacqueline Pichler Hefti1, Denise Sonntag2, Urs Hefti3, Tobias M. Merz4, A. Castro-Rodriguez1.

Hypoxygenia-induced excessive pulmonary vasoconstriction is assumed to be the main cause of life-threatening high altitude pulmonary edema. Decrease of nitric oxide (NO), a potent vasodilator, has been suggested to play a significant role in hypoxygenia-induced vasconstriction. To study alterations of prolonged hypobaric hypoxia, serum samples were drawn from 34 healthy mountaineers up to 6865 m during a Swiss research expedition to mount Muztagh Ata (7549 m) in Western China. Comprehensive metabolomics analysis using a mass spectrometry-based targeted approach revealed a pronounced systemic oxidative stress during high altitude exposure. Detecting more than 390 parameters, a significant increase of lipid peroxidation was shown. Methionine sulfox, determined in relation to methione, furthermore serves as a robust indicator of oxidative stress and showed highly increased values of 30% (mean at 5000m), compared to values of 20% in septic patients. We also found relevant functional impairment of phosphorylase hydrogenase and nitric oxide synthase (NOS), enzymes which both require an oxidation-sensitive co-factor. Consequently, very low levels of NO were found. In addition, significant increase in the serum concentration of vessel tone modifiers such as leukotrienes and prostaglandins were found.

This novel and holistic approach extends the mechanistic understanding of hypoxygenia-related oxidative damage to a biochemical level and unravels underlying biochemical pathways involved in hypoxygenia-induced pulmonary vasoconstriction. Together, we demonstrate further insight into the molecular pathogenesis of hypoxygenia-related disorders.
Oral Presentation
Room 3.1 - 08:30-10:30

MONDAY, SEPTEMBER 26TH 2011

1704 Systemic upregulation of neutrophil α-defensins and serine proteases in neutrophilic asthma
Katherine Baines1,2, Jodie Simpson1,2, Lisa Wood1,3, Rodney Scott1, Peter Gibson1,2,3, Rodney Scott1

Background: The well characterised airway inflammatory phenotypes of asthma include eosinophilic, neutrophilic, mixed eosinophilic/neutrophilic and paucigranulocytic asthma, defined by the proportion of sputum granulocytes. Systemic inflammation is now recognised as an important part of some airway diseases, but the role of systemic inflammation in the pathogenesis of asthma phenotypes remains unknown.

Methods: Induced sputum samples and peripheral blood were collected from participants with asthma (n=36). Airway inflammatory cell counts were performed on induced sputum and inflammatory phenotype assigned based on the airway eosinophil and neutrophil cutoffs of 3% and 61% respectively. Gene expression profiles were generated (Illumina HumanE6 V3) from whole blood RNA and analysed using GeneSpring GX11.

Results: There were 6 genes classified as differentially expressed between the 4 asthma phenotypes including the α-defensins (DEFA1) 1, 1B, 3, and 4, neutrophil proteases cathespin G (CTSG) and elastase (ELA2). Systemic expression of DEFA1, 1B, 3, 4, CTSG and ELA2 was significantly higher in the neutrophilic asthma phenotype. Microarray results were successfully validated using real-time PCR. Plasma elastase was significantly elevated in people with neutrophilic airway asthma phenotype. Microarray results were successfully validated using real-time PCR. Plasma elastase was significantly elevated in people with neutrophilic airway asthma phenotype.

Conclusion: This demonstrates a systemic inflammatory component in neutrophilic asthma that further differentiates this from other asthma phenotypes, and indicates different mechanisms.

1705 DNA copy number alterations in squamous metaplastic lesions predict lung cancer
Robert van Boerdonk1, Thomas Sutedja2, Peter Snijders1, Emilie Reinen1, Saskia Wiltig1, Mark van die Wel1, Frederik Thumissen1, Sylvia Duin1, Clarissa Koo1,2, Bawa Yistra1, Chris Meijer1, Gerrit Meijer1, Karrien Gréurm1, Johannes Daniels2, Pieter Postma2, Egbert Smits1, Danielle Heideman1.

Introduction: Distinguishing SCC from AC has become crucial for tailored therapies of NSCLC. Many patients are inoperable at the time of diagnosis of NSCLC, >65% of the diagnoses are performed in small biopsies (Bx). The “IASLC/ATS/ERS international multidisciplinary classification of lung adenocarcinoma” (Travis W.D., Brambilla E. et al. JTO 2011; 6:244-85) firstly includes diagnostics in Bx in addition to resection specimen. We investigated the expression of IHC markers in a TMA simulating Bx.

Materials and methods: The IHC markers CK5/6, p63, desmocollin-3, CK7, TTF1, and napsin were investigated in a TMA from a primary cohort of 1005 patients with resected NSCLC.

Results: For SCC, desmocollin-3 showed the highest, CK5/6 a medium, and p63 the lowest specificity. The sensitivity of desmocollin-3 was similar to the combined sensitivity of CK5/6 and p63. Desmocollin-3 was expressed in about 85%, CK5/6 and p63 in >90% of all SCC.

For AC, TTF1 and napsin revealed a considerably higher specificity than CK7. The sensitivity of napsin did not exceed the combined specificity of CK7 and TTF1.

Conclusions: To spare tumor tissue for further (e.g. molecular) analyses, diagnostic algorithms for NSCLC Bx must be established. If histology alone cannot distinguish between SCC and AC, a combination of TTF1, napsin, CK5/6 and desmocollin-3 can serve as initial diagnostic marker panel. CK7 and p63 could be used subsequently, if necessary, because of lower specificity. Currently a TMA of 300 further NSCLC is investigated, data from all 1300 NSCLC will be presented.

1706 Differentiation between squamous cell carcinoma (SCC) and adenocarcinoma (AC): Expression of immunohistochemical (IHC) markers in a tissue microarray (TMA) of >1000 NSCLC
Philipp A. Schnabl1, Esther Herpel1, Thomas Moley2, Hans Hoffmann3, Peter Schirmacher4, Arne Warth5, Institute of Pathology, University Clinics, Heidelberg, Germany; 5Thoracic Surgery, Thoraxklinik Heidelberg at the University Clinics, Heidelberg, Germany.

Background: The IHC markers CK5/6, p63, desmocollin-3, CK7, TTF1, and napsin were investigated in a TMA from a primary cohort of 1005 patients with resected NSCLC.

Results: For SCC, desmocollin-3 showed the highest, CK5/6 a medium, and p63 the lowest specificity. The sensitivity of desmocollin-3 was similar to the combined sensitivity of CK5/6 and p63. Desmocollin-3 was expressed in about 85%, CK5/6 and p63 in >90% of all SCC.

Conclusions: To spare tumor tissue for further (e.g. molecular) analyses, diagnostic algorithms for NSCLC Bx must be established. If histology alone cannot distinguish between SCC and AC, a combination of TTF1, napsin, CK5/6 and desmocollin-3 can serve as initial diagnostic marker panel. CK7 and p63 could be used subsequently, if necessary, because of lower specificity. Currently a TMA of 300 further NSCLC is investigated, data from all 1300 NSCLC will be presented.