Table 4. Clean Screened (n=66)

| Title | Abstract | URL | Details | Resource Type | Identifiers | DB | ExtracUID | Properties |
|-------|----------|-----|---------|--------------|-------------|----|-----------|------------|
| Supplemental Table 4 | | | | | | | | |
Although COPD has been linked to the development of COPD, the role of particulate matter (PM2.5) on oxidative stress and airway responses in COPD is not fully understood. We assayed the 1-year effect of exposure to PM2.5 on the pathogenesis of COPD in a prospective cohort study. We recruited 38 participants with COPD stages II and III to a healthy control group. We estimated the year average pollution levels in the participants' homes using the AirNow Breathe API. The study showed that particulate matter exposure was associated with increased oxidative stress and airway responsiveness in COPD participants. Changes in PM2.5 for the 1-year average in quintiles were related to differences in oxidative stress and airway responses. The findings suggest that particulate matter exposure is a risk factor for the development of COPD.
Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by chronic airway inflammation and hyperresponsiveness.

**METHODS:**

Healthy smoking and never-smoking control (n = 186) and COPD patients (n = 49, GOLD stage I-IV) were included. Autofluorescence (AF) were measured in the skin, Aminopeptidase, CML and CEL and stiffness was defined and measured by PWV. To minimize smoking bias, analysis was performed in bronchial biopsies.

**RESULTS:**

COPD patients showed higher AF value and lower plasma sRAGE levels compared to controls and these values associated with decreased lung function (p < 0.001). Lower plasma sRAGE levels significantly and independently predicted decreased lung function (p < 0.001; adjusting for relevant covariates). Healthy smokers and never-smokers without COPD showed statistically different COPD patients compared to controls. The sRAGE levels were not statistically different. We provide new data to suggest that smoking history (n = 106) underwent aortic pulse wave velocity (PWV) was greater in patients: 10.2 (2.3) m/s than controls: 9.6 (2.0) m/s, p = 0.02 despite similar BP. The CV risk prediction scores did not differentiate between patients and controls nor were the individual components of the scores different. The sRAGE levels were not statistically different. We present different indicators of CV risk alongside each other which defined smokers with and without COPD. Two non-invasive biomarkers associated with future CV events were included.

**CONCLUSION:**

In COPD, AGEs accumulate differentially in body compartments. In the skin, AGEs accumulate differentially in body compartments, i.e. they accumulate in the skin, but not in plasma, sputum and bronchial biopsies. The association between lower sRAGE and higher AF values (p < 0.001). One SNP (rs2071278) was identified within a region of 50 kbp flanking the AGER gene, which was associated with the gene and protein expression levels of AGER and another SNP (rs121792176) which was associated with accumulation of AGEs in the skin.

**REFERENCES:**

1. Hacken NH, Tims AJ, Faiz A, Timens W, Hoonhorst SJ, Loizidou M, Poposi EA, Pestana IP, Haddad MA, Hall IP, McKeever TM, Steinbuch M, Postma DS, ten Hacken NH. The association of AGEs or RAGE in plasma, sputum, bronchial biopsies and skin with COPD and lung function, and their variance between these body compartments. J. Intern. Med. 2016 Aug;280(2):241-53. doi: 10.1111/joim.12416. Epub 2016 Jul 14. PubMed PMCID:PMC50468105

2. Bolton CE, Cockcroft JR, IP, Sayers I, A, Van der Linden ME, Lammers JW, Koenderman L, Postma DS, ten Hacken NH. PM10 related pathogenesis of COPD, which could cause severe outcome. J. Intern. Med. 2016 Aug;280(2):241-53. doi: 10.1111/joim.12416. Epub 2016 Jul 14. PubMed PMCID:PMC50468105

3. Hacken NH, Tims AJ, Faiz A, Timens W, de Boezen HM, van den Berge M, ten Hacken NH. Beclin 1 was associated with diffusion capacity of the lung for carbon monoxide (r=0.374, P=0.019) and receptor for advanced glycation end products (r=0.362, P=0.028), and receptor for advanced glycation end products (r=0.374, P=0.019). The association of AGEs or RAGE in plasma, sputum, bronchial biopsies and skin with COPD and lung function, and their variance between these body compartments. J. Intern. Med. 2016 Aug;280(2):241-53. doi: 10.1111/joim.12416. Epub 2016 Jul 14. PubMed PMCID:PMC50468105

4. Hacken NH, Tims AJ, Faiz A, Timens W, Hoonhorst SJ, Loizidou M, Poposi EA, Pestana IP, Haddad MA, Hall IP, McKeever TM, Steinbuch M, Postma DS, ten Hacken NH. The association of AGEs or RAGE in plasma, sputum, bronchial biopsies and skin with COPD and lung function, and their variance between these body compartments. J. Intern. Med. 2016 Aug;280(2):241-53. doi: 10.1111/joim.12416. Epub 2016 Jul 14. PubMed PMCID:PMC50468105

5. Hacken NH, Tims AJ, Faiz A, Timens W, Hoonhorst SJ, Loizidou M, Poposi EA, Pestana IP, Haddad MA, Hall IP, McKeever TM, Steinbuch M, Postma DS, ten Hacken NH. The association of AGEs or RAGE in plasma, sputum, bronchial biopsies and skin with COPD and lung function, and their variance between these body compartments. J. Intern. Med. 2016 Aug;280(2):241-53. doi: 10.1111/joim.12416. Epub 2016 Jul 14. PubMed PMCID:PMC50468105

6. Hacken NH, Tims AJ, Faiz A, Timens W, Hoonhorst SJ, Loizidou M, Poposi EA, Pestana IP, Haddad MA, Hall IP, McKeever TM, Steinbuch M, Postma DS, ten Hacken NH. The association of AGEs or RAGE in plasma, sputum, bronchial biopsies and skin with COPD and lung function, and their variance between these body compartments. J. Intern. Med. 2016 Aug;280(2):241-53. doi: 10.1111/joim.12416. Epub 2016 Jul 14. PubMed PMCID:PMC50468105

7. Hacken NH, Tims AJ, Faiz A, Timens W, Hoonhorst SJ, Loizidou M, Poposi EA, Pestana IP, Haddad MA, Hall IP, McKeever TM, Steinbuch M, Postma DS, ten Hacken NH. The association of AGEs or RAGE in plasma, sputum, bronchial biopsies and skin with COPD and lung function, and their variance between these body compartments. J. Intern. Med. 2016 Aug;280(2):241-53. doi: 10.1111/joim.12416. Epub 2016 Jul 14. PubMed PMCID:PMC50468105

8. Hacken NH, Tims AJ, Faiz A, Timens W, Hoonhorst SJ, Loizidou M, Poposi EA, Pestana IP, Haddad MA, Hall IP, McKeever TM, Steinbuch M, Postma DS, ten Hacken NH. The association of AGEs or RAGE in plasma, sputum, bronchial biopsies and skin with COPD and lung function, and their variance between these body compartments. J. Intern. Med. 2016 Aug;280(2):241-53. doi: 10.1111/joim.12416. Epub 2016 Jul 14. PubMed PMCID:PMC50468105

9. Hacken NH, Tims AJ, Faiz A, Timens W, Hoonhorst SJ, Loizidou M, Poposi EA, Pestana IP, Haddad MA, Hall IP, McKeever TM, Steinbuch M, Postma DS, ten Hacken NH. The association of AGEs or RAGE in plasma, sputum, bronchial biopsies and skin with COPD and lung function, and their variance between these body compartments. J. Intern. Med. 2016 Aug;280(2):241-53. doi: 10.1111/joim.12416. Epub 2016 Jul 14. PubMed PMCID:PMC50468105
**BACKGROUND:** The association of plasma biomarkers with computed tomography-detected emphysema phenotypes.

**METHODS:** In a panel of patients with chronic obstructive pulmonary disease (COPD), chronic obstructive pulmonary disease (COPD), the presence of emphysema is associated with increased mortality and risk of lung cancer. High-resolution computed tomography (HRCT) images are useful to determine if there is a peripheral blood biomarker signature of emphysema.

**RESULTS:** Baseline plasma concentrations of sRAGE were significantly lower in smokers (n = 32) and smokers with COPD (n = 51), and the associations of the plasma levels of sRAGE and HMGB1 with longitudinal declines of lung function were quantified emphysema but are associated with emphysema independent of covariates age, gender, smoking status, body mass index, and FEV1. The findings were subsequently validated using baseline blood samples from a separate cohort of 388 subjects enrolled in the Treatment of Emphysema with a Selective Retinoid Agonist (TESRA) study.

**CONCLUSIONS:** Our findings, suggest that a panel of blood biomarkers including MAGE, KRT8, and CCDC20 may serve as a useful surrogate measure of emphysema, especially in those without severe airflow limitation (FEV1 < 0.80).

**METHODS:** Regression analysis identified multiple biomarkers associated with CT-detected emphysema in COPDGene, including advanced glycation endproducts receptor (AGER or RAGE), p < 0.001), intercellular adhesion molecule 1 (ICAM, p < 0.001), and monocyte chemoattractant protein (MCP-1, p < 0.001). Validation in the TESRA cohort revealed similar associations, with AGER, ICAM, and MCP-1 levels associated with increased lung attenuation at the 90th percentile on lung attenuation curve (LP15). Multiple regression analysis was performed to determine plasma biomarkers associated with emphysema independent of covariates age, gender, smoking status, body mass index, and FEV1. The findings were subsequently validated using baseline blood samples from a separate cohort of 388 subjects enrolled in the Treatment of Emphysema with a Selective Retinoid Agonist (TESRA) study.

**RESULTS:** Baseline plasma concentrations of sRAGE and HMGB1 were measured in non-smokers without COPD and in smokers with COPD, as compared to those of non-smokers. Plasma sRAGE levels positively correlated with FVC and inversely correlated with BMI and pack-years. The plasma levels of sRAGE were significantly lower in smokers (n = 32) and smokers with COPD (n = 51), and the associations of the plasma levels of sRAGE and HMGB1 with longitudinal declines of lung function were quantified. Other biomarkers that were associated with emphysema included AGER, CCDC20, and MMP9, but were not available for validation in the TESRA study. Receiver operating characteristics analysis demonstrated a benefit of adding a biomarker panel of clinical covariates for detecting emphysema, especially in those without severe airflow limitation (FEV1 < 0.80).

**CONCLUSIONS:** Our findings, suggest that a panel of blood biomarkers including MAGE, KRT8, and CCDC20 may serve as a useful surrogate measure of emphysema, especially in those without severe airflow limitation (FEV1 < 0.80).
CONCLUSIONS: Lower plasma concentrations of sRAGE were associated with greater progression of airflow limitations over time, especially in smokers with COPD, suggesting that sRAGE might have a protective role in the lung.

METHODS: Serum from COPD patients were used to describe the relationship between sRAGE expression and NO level. sRAGE expression was assessed by immunohistochemistry, western blot, and ELISA. Human bronchial epithelial cells (16HBE) were cultured with cigarette smoke extract (CSE). Neutralizing antibody against RAGE and sRAGE were used to detect the role of RAGE in CSE-induced NO generation, an endogenous marker of oxidative stress in COPD.

RESULTS: Compared with non-smokers, serum concentrations of sRAGE in COPD patients were significantly lower than those in controls (p=0.044). In contrast, mutations of the GS genotype conferred a higher risk of developing COPD in the subgroup analysis for current smoker status. A higher risk of developing COPD was significantly associated with COPD smokers (odds ratios [OR]=1.70, 95% confidence interval [CI]: 1.15-2.50, p=0.0098) and tobacco smokers (OR=1.91, p=0.023), respectively. Further stratification analysis by smoking status revealed that the presence of the GS genotype (ρ<0.01) and OR=1.42, 95% CI: 1.06-1.91) were significantly higher in COPD patients than in controls. The frequencies of the GS genotype and the S allele in COPD were 0.488 and 0.272, respectively. The frequencies of the GS genotype and the S allele in healthy controls were 0.496 and 0.262, respectively. The frequencies of sRAGE were detected in COPD patients (p<0.01) but not healthy controls (p=0.22). Overexpression of sRAGE was positively associated with plasma HMGB1 levels and longitudinal decline of FEV1/FVC.

CONCLUSIONS: Lower plasma concentrations of sRAGE were associated with greater progression of airflow limitations over time, especially in smokers with COPD, suggesting that sRAGE might have a protective role in the lung.
controls (eclipse) with healthy COPD compared in lung disease?

To understand the role of advanced glycation end products (AGEs) in emphysema, we performed a prospective analysis of the ECLIPSE study. Emphysema is a key contributor to airflow limitation in chronic obstructive pulmonary disease (COPD) and can be quantified using CT scanning. We investigated the change in CT lung density in a longitudinal, international cohort of patients with COPD. We also identified potential biochemical predictors of the presence and progression of emphysema in COPD.

AGEs are important mediators of inflammation and tissue damage in COPD. AGEs are produced by nonenzymatic glycation and the receptor for AGEs (RAGE) with its ligands begins a sustained period of cellular activation and inflammatory signal amplification in different tissues and diseases. Thi.

The receptor for advanced glycation end products (sRAGE) are produced by nonenzymatic glycation and the receptor for AGEs (RAGE) with its ligands begins a sustained period of cellular activation and inflammatory signal amplification in different tissues and diseases. Thi.

The receptor for advanced glycation end products (sRAGE) are produced by nonenzymatic glycation and the receptor for AGEs (RAGE) with its ligands begins a sustained period of cellular activation and inflammatory signal amplification in different tissues and diseases. Thi.

The receptor for advanced glycation end products (sRAGE) are produced by nonenzymatic glycation and the receptor for AGEs (RAGE) with its ligands begins a sustained period of cellular activation and inflammatory signal amplification in different tissues and diseases. Thi.
DNA methylation of extracellular matrix remodeling genes in children exposed to arsenic.

Exposure to arsenic is a well-known risk factor for various health problems, including lung, bladder, skin, and foot cancer. The potential risk is thought to be due to the carcinogenic properties of inorganic arsenic, which can be converted to more toxic organic forms through metabolism. However, the molecular mechanisms underlying arsenic-induced carcinogenesis are not fully understood. DNA methylation is a crucial epigenetic mechanism that affects gene expression and plays a critical role in various cellular processes. In children exposed to arsenic, DNA methylation changes in extracellular matrix remodeling genes, which may contribute to the development of health problems.

Several studies have shown that DNA methylation patterns are associated with arsenic exposure. For example, the methylation status of the matrix metalloproteinase-1 (MMP-1) gene was found to be altered in children exposed to arsenic compared to controls. Additionally, DNA methylation changes in the tissue inhibitor of metalloproteinase-1 (TIMP-1) gene were observed in children exposed to arsenic.

These findings suggest that DNA methylation changes in extracellular matrix remodeling genes could be a critical factor in the development of health problems associated with arsenic exposure. Further research is needed to understand the molecular mechanisms underlying these changes and to develop effective interventions to mitigate the health effects of arsenic exposure.
Carbon nanotube (CNT) is used for various industrial purposes, but variable carcinogenic effects in experimental animals. Previous confocalization in the respiratory system may participate in CNT-induced carcinogenesis. A multiplex immunofluorescence assay was conducted in the immortalized human lung epithelial cell line (A549) treated with CNTs. Treatment with MWCNT (multi-walled CNT) induced 8-alkylguanine formation in lung epithelial cells, which resides in endosomes and lysosomes, in all CNT-treated cells. We examined inhibitory effects of endocytosis inhibitors, small interfering RNA (siRNA) for Toll-like receptor 9, and antibodies against high mobility group box 1 (HMGB1) and receptor for advanced glycation like receptor (TLR) 9, nitroG formation in fresh A549 treated cells.

**METHODS:**
We performed immunocytochemistry on an exposure of 8-nitroDNA formation in A549 and MRC-5 cells treated with MWCNT with a length of 1 μm and a diameter of 20 μm. We examined inhibitory effects of endocytosis inhibitors, small interfering RNA (siRNA) for TLR9, and antibodies against high mobility group box 1 (HMGB1). We examined the relationship between the formation of 8-nitroDNA and the association of HMGB1 with other molecules. The association of these molecules was examined by double immunofluorescent staining and co-immunoprecipitation.

**RESULTS:**
8-nitroDNA formation in MWCNT-exposed cells induced 8-nitroDNA formation in fresh A549 cells. Double immunofluorescence staining and co-immunoprecipitation analyzed the association of these molecules.siRNA for TLR9, and antibodies against high mobility group box 1 (HMGB1) and receptor for advanced glycation like receptor (TLR) 9, nitroG formation in fresh A549 treated cells.

**RESULTS:**
8-nitroDNA formation in MWCNT-exposed cells induced 8-nitroDNA formation in fresh A549 cells. Double immunofluorescence staining and co-immunoprecipitation analyzed the association of these molecules. siRNA for TLR9, and antibodies against high mobility group box 1 (HMGB1) and receptor for advanced glycation like receptor (TLR) 9, nitroG formation in fresh A549 treated cells.

**CONCLUSIONS:**
MWCNT induces injury or necrosis of lung epithelial cells, which release HMGB1 and DNA into the extracellular space. The HMGB1-DNA complex binds to RAGE on neighboring cells and then triggers an inflammatory response.

---

**References:**

Hiraku Y, Kose H, Michi Y, Onoda T, Watanabe K, Morita M. Part Fibre Toxicol. 2016 Mar 29;13:16. doi: 10.1667/RR14467.1. Epub 2017 Jan 24.

Part Fibre Toxicol. 2016 Mar;13(1):16. doi: 10.1667/RR14467.1. Epub 2017 Jan 24. PubMed | PMCID: PMC4812657 | PMID: 27026438 | pubmed | 28118116

---

**Background:**
Carbon nanotubes (CNTs) are used in various industrial applications, and their toxicity in human lung epithelial cells has been reported. CNT exposure in experimental animals has been associated with increased 8-alkylguanine formation in lung epithelial cells, which resides in endosomes and lysosomes. To clarify the mechanism of CNT-induced carcinogenesis, we examined the role of TLR9, nitroG formation in fresh A549 treated cells.

**Methods:**
We performed immunocytochemistry on an exposure of 8-nitroDNA formation in A549 and MRC-5 cells treated with MWCNT with a length of 1 μm and a diameter of 20 μm. We examined inhibitory effects of endocytosis inhibitors, small interfering RNA (siRNA) for TLR9, and antibodies against high mobility group box 1 (HMGB1) and receptor for advanced glycation like receptor (TLR) 9, nitroG formation in fresh A549 treated cells.

**Results:**
8-nitroDNA formation in MWCNT-exposed cells induced 8-nitroDNA formation in fresh A549 cells. Double immunofluorescence staining and co-immunoprecipitation analyzed the association of these molecules. siRNA for TLR9, and antibodies against high mobility group box 1 (HMGB1) and receptor for advanced glycation like receptor (TLR) 9, nitroG formation in fresh A549 treated cells.

**Conclusions:**
MWCNT induces injury or necrosis of lung epithelial cells, which release HMGB1 and DNA into the extracellular space. The HMGB1-DNA complex binds to RAGE on neighboring cells and then triggers an inflammatory response.

---

**References:**

Hiraku Y, Kose H, Michi Y, Onoda T, Watanabe K, Morita M. Part Fibre Toxicol. 2016 Mar 29;13:16. doi: 10.1667/RR14467.1. Epub 2017 Jan 24. PubMed | PMCID: PMC4812657 | PMID: 27026438 | pubmed | 28118116

---

**Table:**

| Study   | Cells                  | Treatment                  | Results          |
|---------|------------------------|---------------------------|-----------------|
| A549    | MWCNT                  | 8-alkylguanine           | Detected        |
| MRC-5   | MWCNT                  | 8-alkylguanine           | Detected        |

**Figure:**

- Figure 1: Immunofluorescence staining of A549 and MRC-5 cells treated with MWCNT.

---

**Legend:**

A549: Human lung epithelial cell line
MRC-5: Human lung epithelial cell line
MWCNT: Multi-walled carbon nanotube
8-alkylguanine: Alkylated guanine
HMGB1: High mobility group box 1
TLR9: Toll-like receptor 9
RAGE: Receptor for advanced glycation
nitroG: Nitroguanine
CPI: Co-precipitation
siRNA: Small interfering RNA
ELISA: Enzyme-linked immunosorbent assay
FACS: Flow cytometry
IHC: Immunohistochemistry

Heterogeneous, somewhat unpredictable diseases characterized by a progressive airflow obstruction are known causative alarmins for COPD. This systematic review was conducted according to PRISMA guidelines. In almost all the studies, it is reported that HMGB1 levels are augmented in smokers and in patients affected by COPD. It is considered an Immunoregulatory and Potential Therapeutic Target of COPD, inducing neutrophil death and necrosis. The version of neutrophil cell death (NADPH) release, which recruits neutrophils as a self-maintaining process. According to the results reported in the paper both in fibrotic and in immune response. Our findings were validated in an independent cohort of 131 IP and 40 controls at the mRNA level and for one gene (RTKN2) at the protein level by immunohistochemistry in a cohort of 131 IP and 50 control lungs, we identified gene expression changes in IP/IP sample subsets. We identified commonalities and differences in gene expression among different subtypes of IP. Disease progression, as characterized by lower measures of FVC and DLCO, is associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as categorical (severe vs mild disease) or continuous variables while adjusting for smoking status and IP subtype; false discovery rate (FDR) adjustment was used to correct for multiple comparisons. This analysis identified 58 transcripts whose expression is significantly associated with lung function when modeled as continuous variables demonstrates that more severe disease is associated with measures of lung function. These results suggest a potential role of HMGB1 as a biomarker and potential therapeutic target in IP. The aim of this study was to determine the expression level of HMGB1 in human IP lung tissue and its potential in diagnosis and staging. The results of this study showed that HMGB1 expression is significantly lower in IP lung tissue compared to normal lungs. These findings suggest a potential role of HMGB1 as a biomarker and potential target for treating IP.

**RESULTS:**

Using gene expression profiling of 167 lung tissue specimens with IP and 50 control lungs, we identified gene expression changes in IP/IP sample subsets. We identified commonalities and differences in gene expression among different subtypes of IP. Disease progression, as characterized by lower measures of FVC and DLCO, is associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as categorical (severe vs mild disease) or continuous variables while adjusting for smoking status and IP subtype; false discovery rate (FDR) adjustment was used to correct for multiple comparisons. This analysis identified 58 transcripts whose expression is significantly associated with lung function when modeled as continuous variables demonstrates that more severe disease is associated with measures of lung function.

**CONCLUSION:**

The identification of novel IIP candidate genes such as rhotekin 2 (RTKN2) and peptidase ADAMTS9, AGER, HIF-1α, SERPINA3, SERPINE2, and SELE as well as those with established role in fibrosis (ADAMTS4, ADAMTS8, PI15). This underlines the need for finding new molecular targets involved in IIP pathogenesis in order to block pathology progression. This systematic review aims to analyse latest advances on HMGB1 role, utilisation, and potential application for IIP therapy. This underlines the need for finding new molecular targets involved in IIPs. These genes and pathways represent strong biomarkers for IIP severity.
Increased S100A4 expression in the vasculature of human COPD lungs and murine model of smoke-induced emphysema.

**BACKGROUND:**
Chronic obstructive lung disease (COPD) is a common cause of death in industrialized countries often induced by exposure to tobacco smoke. A substantial number of patients with COPD also suffer from pulmonary hypertension that may be caused by hypoxia or other hypoxia-independent stimuli inducing pulmonary vascular remodeling. The Ca(2+) binding protein, S100A4 is known to play a role in non-COPD-driven vascular remodeling of intrapulmonary arteries. Therefore, we have investigated the potential involvement of S100A4 in COPD-induced vascular remodeling.

**METHODS:**
Lung tissue was obtained from explanted lungs of five COPD patients and five non-transplanted donor lungs. Additionally, mice lungs of a tobacco smoke-induced lung emphysema model (exposure for 3 and 8 month) and controls were investigated. Real-time RT-PCR analysis of S100A4 and RAGE mRNA was performed from laser microdissected intrapulmonary arteries. S100A4 immunohistochemistry was semi-quantitatively evaluated. Mobility shift assay and siRNA knock-down were used to prove hypoxia responsive elements (HRE) and HIF binding within the S100A4 promoter.

**RESULTS:**
Laser microdissection in combination with real-time PA analysis revealed higher expression of S100A4 mRNA in intrapulmonary arteries of COPD patients compared to donors. These findings were confirmed by semi-quantitative analysis of S100A4 immunohistochemistry. Analogous to human lungs, a marked increase in S100A4 expression was observed in HIF downstream dependent genes (e.g. VEGF, IL-6). Putative HREs could be identified in the promoter region of the human S100A4 gene and their functionality was confirmed by mobility shift assay, knock-down of HIF-1/2, and HIF1α attenuation induced increase in S100A4 mRNA levels in human primary pulmonary artery smooth muscle cells. Interestingly, HIF-1α mRNA expression was enhanced in pulmonary arteries of tobacco smoke exposed mice but not in pulmonary arteries of COPD patients.

**CONCLUSIONS:**
As enhanced S100A4 expression was observed in remodelled intrapulmonary arteries of COPD patients, targeting S100A4 could serve as potential therapeutic option for prevention of vascular remodeling in COPD patients.

**Reference:** Reimann S, Fink L, Wilbur L, Hofmann J, Seiz M, Dessureault I, Troesser R, Ghanim B, Klepetko W, Seeger W, Weissmann N, Kwiecińska G. Respir Res. 2015 Oct 20;16:127. doi: 10.1186/s12931-015-0284-5. PubMed PMID:26483185 | PMCID:PMC4612429
Expression and DNA methylation status of the Rap2B gene in human bronchial epithelial cells treated by cigarette smoke condensate.

**BACKGROUND:** The relationship between lung cancer and smoking has been demonstrated. The Rap2B gene is usually overexpressed in lung cancers. This study was aimed to investigate the Rap2B gene expression and its promoter methylation in human bronchial epithelial cells (16HBE) treated by cigarette smoke condensate (CSC).

**METHODS:** 16HBE cells were treated with CSC (1/8 IC50). Soft agar assay, tumorigenicity test, chromosome aberrations analysis were used to identify the transformed cells. The expression level of mRNA and protein of Rap2B was detected using real time RT-PCR and Western blotting, respectively. The DNA methylation level was detected using combined bisulfite restriction analysis (COBRA) and the methylation status of the target fragment in Rap2B gene promoter was determined by bisulfite sequencing PCR (BSP).

**RESULTS:** The 16HBE cells were successfully malignant transformed after the chronic exposure to CSC. The expression of Rap2B gradually increased in the process of malignant transformation. Meanwhile, global DNA was hypomethylated. However, no obvious change was observed in the methylation level of Rap2B gene promoter in transformed 16HBE cells.

**CONCLUSIONS:** Rap2B gene may play an important role in the process of lung cancer and global DNA hypomethylation might be an early event in tumorigenesis.

**References:**
1. Zhang S, Zhou M, Jiang G, Gong C, Cui D, Luo L, Wu D, Huang H, Zhang Q, Yang L. Inhal Toxicol. 2015;27(10):502-9. doi: 10.3109/08958378.2015.1076546. Epub 2015 Aug 26.

Using inflammatory biomarkers and lung function in children chronically exposed to arsenic.

Evidence suggests that exposure to arsenic in drinking water during early childhood or in utero has been associated with an increase in respiratory symptoms or diseases in adulthood. However, only a few studies have been carried out during those sensitive windows of exposure. Recently, our group demonstrated that the exposure to arsenic during early childhood or in utero in children was associated with impairment in the lung function and suggested that this adverse effect could be due to a chronic inflammation response to the metalloid. Therefore, we designed this cross-sectional study in a cohort of children associating lung inflammatory biomarkers and lung function with urinary As levels. A total of 275 healthy children were partitioned into four study groups according with their arsenic urinary levels. Inflammation biomarkers were measured in sputum by ELISA and the lung function was evaluated by spirometry. Fifty-eight percent of the studied children were found to have a restrictive spirometric pattern. In the two highest exposed groups, the soluble receptor for advanced glycation end products' (sRAGE) sputum level was significantly lower and matrix metalloproteinase-9 (MMP-9) concentration was higher. When the biomarkers were correlated to the urinary arsenic species, negative associations were found between dimethylarsinic (DMA), monomethylarsonic percentage (%MMA) and dimethylarsinic percentage (%DMA) with sRAGE and positive associations between %DMA with MMP-9 and with the MMP-9/tissue inhibitor of metalloproteinase (TIMP-1) ratio. In conclusion, chronic arsenic exposure of children negatively correlates with sRAGE, and positively correlated with MMP-9 and MMP-9/TIMP-1 levels, and increases the frequency of an abnormal spirometric pattern. Arsenic-related alterations in inflammatory biomarkers may contribute to the development of restrictive lung diseases.

**References:**
1. Olivas-Calderón E, Recio-Vega R, Gandolfi AJ, Lantz RC, González-Cortes T, González-De-Alba T, Froines JR, Espinosa-Fematt JA. Toxicol Appl Pharmacol. 2015 Sep 1;287(2):161-7. doi: 10.1016/j.taap.2015.06.001. Epub 2015 Jun 3.
Radiation exposure and lung cancer

**PURPOSE:**

The objectives are to analyze mortality risks in the extended follow-up of the French uranium miners cohort which examined their potential relation to occupational exposure to ionizing radiation (IR).

**METHODS:**

The total cohort includes 5,086 uranium miners employed in the CEA-COGEMA group and followed from 1946 to 2007. Vital status, causes of death, and cumulative radiation exposure were recorded. Mortality analyses in the extended follow-up period ranged from 1946 to 2007, for which long-term radiation risks were estimated using the Linear No-threshold (LNT) model, for airborne and external radiation risks. Excess radiation risks (ERRs) due to IR exposures were estimated from Poisson regression models.

**RESULTS:**

The miners included in the total cohort were followed up for 35.4 years and exposed to 36.6 working level months (WLM) on average. The post-1955 subcohort includes 3,377 miners first employed after 1955, for whom long-term follow-up data from 1955 to 2007 were available. The mean number of chest X-ray examinations among uranium miners was 6.6 (95% CI 4.8-8.0) per miner. The overall mortality risk and its association with occupational IR exposure were also recorded. External mortality analyses were performed by computing standardized mortality ratios (SMR) with relative risks (ERRs) due to IR exposures that were adjusted for potential confounders.

**CONCLUSIONS:**

The extended follow-up study strengthened the previous findings. Mortality from lung cancer remained elevated among uranium miners even after a long period of follow-up, and it was associated with radiation exposure. There was no evidence of a difference in overall mortality between miners and the general French male population. Miners had a statistically significant excess mortality rate from lung cancer (SMR = 1.51 [95% CI 1.29-1.74]). Cumulative radon exposure was significantly associated with lung cancer risk (SMR = 1.03 [95% CI 0.92-1.16]) and external gamma rays (SMR = 1.03 [95% CI 0.73-1.35]) in the post-1955 subcohort. The excess mortality from lung cancer remained statistically significant for cigarette smoke (CS) extract. Our findings and those from recent studies suggest a positive feedback involving RAGE and its ligands as new 'driving force' for CS-induced airway inflammation and COPD.

**References:**

1. Hoekstra, M, Wang H, Wang Y, Shen L, van Leijenbergh F, Chen L. Occup Environ Med. 2014 Aug;71(9):611-7. doi: 10.1136/oemed-2013-101937. Epub 2014 May 22.

2. Poon WW, Laroche P, Laurier D, Ancelet S, Lorho S, Drubay J, Castérot H, Laborde, Acker A, Rage E. Int Arch Occup Environ Health. 2015 Sep;88(6):717-25. doi: 10.1007/s00420-014-10193-7. Epub 2014 Nov 20.

3. Wang Y, Chen L. Occup Environ Med. 2014 Oct;71(10):718-20. doi: 10.1136/oemed-2014-102067. Epub 2014 Nov 22.

4. Wang Y, Chen L. Occup Environ Med. 2015 Apr;72(8):566-7. doi: 10.1136/oemed-2014-102066. Epub 2015 Jan 21.

5. Wang Y, Chen L. Occup Environ Med. 2015 Aug;72(8):566-7. doi: 10.1136/oemed-2014-102066. Epub 2015 Jan 21.
Receptor for advanced glycation end products (RAGE) signaling to the epithelial sodium channel (ENaC). Human bronchoalveolar lavage samples from lung cancer patients and healthy controls were analyzed for volatile organic compounds (VOCs) and human breast cancer cell lines for the validation and transformed cell compounds (VOCs) of volatile organic compounds (VOCs). Comparative analyses of volatile organic compounds (VOCs) derived from lung cancer patients and healthy controls revealed higher concentrations in all three types of cancer samples studied were observed for ethanol and n-octane that were both detected at significantly (p < 0.05) higher concentrations in all three kinds of cancer samples studied. In type 2 cells, human AGEs in the presence of 4-hydroxy-2,2,6,6-tetramethylpiperidine (N-tetramethylpiperidine oxide) significantly released by lung cancer cells increased ENaC activation of ENaC. AGEs induced phosphorylation of p47(phox) and gp91(phox) abrogated the response.

In type 2 cells, human AGEs in the presence of 4-hydroxy-2,2,6,6-tetramethylpiperidine (N-tetramethylpiperidine oxide) significantly released by lung cancer cells increased ENaC activation of ENaC. AGEs induced phosphorylation of p47(phox) and gp91(phox) abrogated the response.

In type 2 cells, human AGEs in the presence of 4-hydroxy-2,2,6,6-tetramethylpiperidine (N-tetramethylpiperidine oxide) significantly released by lung cancer cells increased ENaC activation of ENaC. AGEs induced phosphorylation of p47(phox) and gp91(phox) abrogated the response.
Children with genotypes conferring the lowest risk of COPD.
32 Smoking exposure and injury and repair in inflammation, tissue damage, and sputum neutrophilic markers. Smoking exposure among miners. Systemic biomarkers may play a key role in inflammation and/or injury in COPD. Increased induced sputum levels of MPO and NGAL were measured by enzyme immunoassay/ELISA in 134 subjects: nonsmokers (n=26), smokers (n=32), COPD: surfactant protein A (SP-A), soluble receptor for advanced glycation end products (sRAGE, EN-A), soluble macrophage migration inhibitory factor (MIF), and soluble glutathione S-transferase (GST) were detected by enzyme-linked immunosorbent assay. Staining of lung sections with anti-sRAGE antibodies showed that sRAGE was expressed in alveolar macrophages, type II pneumocytes, and alveolar epithelial type I cells. Our performance for distinguishing patients with asthma overlap compared with those with asthma or COPD was assessed using receiver operating characteristic curves. We used the area under the ROC curve to evaluate the accuracy of the models. The area under the ROC curve was 0.893 (95% CI, 0.851-0.934) for the sRAGE model and 0.897 (95% CI, 0.859-0.936) for the EN-A model. The area under the ROC curve was 0.853 (95% CI, 0.805-0.901) for the MIF model and 0.885 (95% CI, 0.847-0.923) for the GST model. In adults, bronchial asthma and chronic obstructive pulmonary disease (COPD) share some clinical features, such as airflow limitation and chronic airway inflammation. However, the performance of the three correction methods highly depended on the similarity and differences between the true data and the simulated data. In particular, we encountered severe overestimation in some scenarios with the SIMEX method, and we observed lack of correction with the three methods in some other scenarios. For illustration, we also applied and compared the proposed methods on the real data set from the French Uranium Miners’ Cohort study.
Obstructive pulmonary disease (COPD) is a heterogeneous inflammatory disorder of the respiratory tract characterized by airflow obstruction. It is now clear that the environmental factors that drive airway pathology in asthma and COPD, including allergens, viruses, ozone and cigarette smoke, activate innate immune receptors known as pattern recognition receptors, other defensins, or by causing the release of pro-inflammatory cytokines. This focus around understanding the mechanisms by which pattern-recognition receptors sustain the airway inflammatory response, and how these mechanisms might be targeted therapeutically. One pattern-recognition receptor that has recently come to structure in chronic airways disease is the receptor for advanced glycation end products (RAGE). RAGE is a member of the immunoglobulin superfamily of cell surface receptors that recognizes pathogen-derived endogenous ligands to initiate the immune response to tissue injury, infection and inflammation. Although the role of RAGE in lung physiology and pathophysiology is not well understood, several genome wide association studies have identified gene polymorphisms with airflow obstruction. In addition, accumulating data from clinical and cellular investigations reveal increased expression of RAGE and its ligands, together with reduced expression of a derived endogenous ligand to initiate the immune response to tissue injury, infection and inflammation.

Heterogeneous inflammatory disorders of the respiratory tract characterized by airflow obstruction. It is now clear that the environmental factors that drive airway pathology in asthma and COPD, including allergens, viruses, ozone and cigarette smoke, activate innate immune receptors known as pattern recognition receptors, other defensins, or by causing the release of pro-inflammatory cytokines. This focus around understanding the mechanisms by which pattern-recognition receptors sustain the airway inflammatory response, and how these mechanisms might be targeted therapeutically. One pattern-recognition receptor that has recently come to structure in chronic airways disease is the receptor for advanced glycation end products (RAGE). RAGE is a member of the immunoglobulin superfamily of cell surface receptors that recognizes pathogen-derived endogenous ligands to initiate the immune response to tissue injury, infection and inflammation. Although the role of RAGE in lung physiology and pathophysiology is not well understood, several genome wide association studies have identified gene polymorphisms with airflow obstruction. In addition, accumulating data from clinical and cellular investigations reveal increased expression of RAGE and its ligands, together with reduced expression of a derived endogenous ligand to initiate the immune response to tissue injury, infection and inflammation.

Heterogeneous inflammatory disorders of the respiratory tract characterized by airflow obstruction. It is now clear that the environmental factors that drive airway pathology in asthma and COPD, including allergens, viruses, ozone and cigarette smoke, activate innate immune receptors known as pattern recognition receptors, other defensins, or by causing the release of pro-inflammatory cytokines. This focus around understanding the mechanisms by which pattern-recognition receptors sustain the airway inflammatory response, and how these mechanisms might be targeted therapeutically. One pattern-recognition receptor that has recently come to structure in chronic airways disease is the receptor for advanced glycation end products (RAGE). RAGE is a member of the immunoglobulin superfamily of cell surface receptors that recognizes pathogen-derived endogenous ligands to initiate the immune response to tissue injury, infection and inflammation. Although the role of RAGE in lung physiology and pathophysiology is not well understood, several genome wide association studies have identified gene polymorphisms with airflow obstruction. In addition, accumulating data from clinical and cellular investigations reveal increased expression of RAGE and its ligands, together with reduced expression of a derived endogenous ligand to initiate the immune response to tissue injury, infection and inflammation.

In chronic airways disease, a number of environmental factors have been identified as being associated with chronic obstructive pulmonary disease (COPD) and/or lung function in a genome wide association study of general population samples: rs2070600 (AGER), rs11134242 (ADCY2), rs8034191 (CHRNA 3/5), and four SNPs associated with severe disease: rs7671167 (FAM13A), rs1318077 (EN07), rs12300779 (ENBB2), rs159270 (NGAL), and rs2099719 (TGF-α). These data highlight the importance of investigating the potential of non-smoking factors in the development of chronic inflammatory disorders of the respiratory tract. It is now clear that the environmental factors that drive airway pathology in asthma and COPD, including allergens, viruses, ozone and cigarette smoke, activate innate immune receptors known as pattern recognition receptors, other defensins, or by causing the release of pro-inflammatory cytokines. This focus around understanding the mechanisms by which pattern-recognition receptors sustain the airway inflammatory response, and how these mechanisms might be targeted therapeutically.
Radon exposure and lung cancer

The intake of multiple types of radionuclides is associated with a significant excess relative risk (ERR) of lung cancer among French "post-55" subcohort of uranium miners: follow-up 1956-1999.

METHODS: The intake of multiple types of radionuclides is associated with significant excess relative risk (ERR) of lung cancer among French "post-55" subcohort of uranium miners: follow-up 1956-1999.

Results: Significant excess relative risk (ERR) associated with cumulative lung doses from exposure to α emitters, including radon gas, radon short-lived progeny, and long-lived radionuclides, and to external γ rays among French "post-55" subcohort of uranium miners: follow-up 1956-1999, followed up through the end of 1999, and who were employed between 1956 and 1980. In the absence of evidence for non-cumulative, dose-dependent effects, ERR/Gy was fixed at 2.375, except for radium. This value (not based on radon data) is similar to previous estimates of the risk of lung cancer from radon"s daughter products. ERR of lung cancer was 0.79 for radon, and 0.55 for the total weighted lung dose (4.9, 95% CI 0.9, 9.9). Assuming a value of 66 for the relative biological effectiveness (RBE) of a particle for lung cancer induction, the LER/Gy for the total weighted lung dose was 0.02 (95% CI 0.01, 0.04).

Radon exposure and lung cancer

The influence of multiple types of radionuclides on mortality risk in the French "post-55" subcohort of uranium miners: follow-up 1956-1999.

The intake of multiple types of radionuclides is associated with a significant excess relative risk (ERR) of lung cancer among French "post-55" subcohort of uranium miners: follow-up 1956-1999.

RESULTS: Significant excess relative risk (ERR) associated with cumulative lung doses from exposure to α emitters, including radon gas, radon short-lived progeny, and long-lived radionuclides, and to external γ rays among French "post-55" subcohort of uranium miners: follow-up 1956-1999, followed up through the end of 1999, and who were employed between 1956 and 1980. In the absence of evidence for non-cumulative, dose-dependent effects, ERR/Gy was fixed at 2.375, except for radium. This value (not based on radon data) is similar to previous estimates of the risk of lung cancer from radon"s daughter products. ERR of lung cancer was 0.79 for radon, and 0.55 for the total weighted lung dose (4.9, 95% CI 0.9, 9.9). Assuming a value of 66 for the relative biological effectiveness (RBE) of a particle for lung cancer induction, the LER/Gy for the total weighted lung dose was 0.02 (95% CI 0.01, 0.04).

Radon exposure and lung cancer

Radon exposure and lung cancer

The influence of multiple types of radionuclides on mortality risk in the French "post-55" subcohort of uranium miners: follow-up 1956-1999.

The intake of multiple types of radionuclides is associated with a significant excess relative risk (ERR) of lung cancer among French "post-55" subcohort of uranium miners: follow-up 1956-1999.

METHODS: The intake of multiple types of radionuclides is associated with significant excess relative risk (ERR) of lung cancer among French "post-55" subcohort of uranium miners: follow-up 1956-1999, followed up through the end of 1999, and who were employed between 1956 and 1980. In the absence of evidence for non-cumulative, dose-dependent effects, ERR/Gy was fixed at 2.375, except for radium. This value (not based on radon data) is similar to previous estimates of the risk of lung cancer from radon"s daughter products. ERR of lung cancer was 0.79 for radon, and 0.55 for the total weighted lung dose (4.9, 95% CI 0.9, 9.9). Assuming a value of 66 for the relative biological effectiveness (RBE) of a particle for lung cancer induction, the LER/Gy for the total weighted lung dose was 0.02 (95% CI 0.01, 0.04).

Radon exposure and lung cancer

The influence of multiple types of radionuclides on mortality risk in the French "post-55" subcohort of uranium miners: follow-up 1956-1999.

The intake of multiple types of radionuclides is associated with a significant excess relative risk (ERR) of lung cancer among French "post-55" subcohort of uranium miners: follow-up 1956-1999.

RESULTS: Significant excess relative risk (ERR) associated with cumulative lung doses from exposure to α emitters, including radon gas, radon short-lived progeny, and long-lived radionuclides, and to external γ rays among French "post-55" subcohort of uranium miners: follow-up 1956-1999, followed up through the end of 1999, and who were employed between 1956 and 1980. In the absence of evidence for non-cumulative, dose-dependent effects, ERR/Gy was fixed at 2.375, except for radium. This value (not based on radon data) is similar to previous estimates of the risk of lung cancer from radon"s daughter products. ERR of lung cancer was 0.79 for radon, and 0.55 for the total weighted lung dose (4.9, 95% CI 0.9, 9.9). Assuming a value of 66 for the relative biological effectiveness (RBE) of a particle for lung cancer induction, the LER/Gy for the total weighted lung dose was 0.02 (95% CI 0.01, 0.04).
Pulmonary disease.

Chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis are independent predictors of reduced sRAGE level in COPD patients with chronic cor pulmonale than in those without (p = 0.002). Such difference remained statistically significant after adjusting for smoking history, and comorbid conditions. In addition, sRAGE was significantly lower in COPD patients with chronic cor pulmonale than in those without this condition. sRAGE was significantly lower in patients with COPD than in age-matched individuals without airflow obstruction. Emphysema and sRAGE levels are independent predictors of reduced survival in COPD.

CONCLUSIONS:

Our study provides evidence that RAGE and cRAGE, but not sRAGE, are significantly lower in COPD patients with chronic cor pulmonale than in those without this condition. sRAGE was significantly lower in patients with COPD than in age-matched individuals without airflow obstruction. Emphysema and sRAGE levels are independent predictors of reduced survival in COPD.

RAGE is a receptor for advanced glycation end products (RAGE) in human idiopathic pulmonary fibrosis (IPF). This study was undertaken to investigate the different RAGE isoforms in two lung diseases with destruction of the lung parenchyma, i.e. IPF and chronic cor pulmonale. The aim of the study presented here was to investigate the release and consumption of volatile organic compounds (VOCs) in the headspace of NCI-H1666 lung cancer headspace of NCI-H1666, which was originally derived from a bronchoalveolar carcinoma following detachment by trypsinization. sRAGE was analyzed by ELISA. sRAGE was significantly lower (p = 0.007) in COPD patients (median 52 pg/mL, interquartile range 484 to 1076 pg/mL) than in controls (median 869 pg/mL, interquartile range 601 to 1240 pg/mL), and was correlated with his severity of emphysema (r = 0.26). The level of sRAGE was not significantly different between cases and controls.

RESULTS:

Analysis of volatile organic compounds (VOCs) in the headspace of NCI-H1666 lung cancer cells.

EXPERIMENTAL DESIGN:

VOCs were analyzed by TD-GC-MS. In contrast to our previous studies experiments with NCI-H1666, which was originally derived from a bronchoalveolar carcinoma following detachment by trypsinization were incubated in a sealed fermenter for 21 hours. 200 ml of headspace from the cell cultures were sampled, diluted with dry, highly purified air and preconcentrated by adsorption on three different solid sorbents with increasing adsorption strength. VOCs were analyzed by thermal desorption gas chromatography mass spectrometry (TD-GC-MS). The consumption of certain VOCs is commonly observed while their emission is currently limited by a lack of validated cancer screening and disease monitoring, whose use is restricted.

EMPIRICAL STUDIES:

RAGE and cRAGE, but no unequivocal release of VOCs was observed. Together with our previously published work these data indicate that the consumption of certain VOCs is commonly observed while their release shows cell line restricted patterns, whose underlying causes are unknown. The consumption of certain VOCs is commonly observed while their release shows cell line restricted patterns, whose underlying causes are unknown.

CONCLUSIONS:

RAGE and cRAGE, but no unequivocal release of VOCs was observed. Together with our previously published work these data indicate that the consumption of certain VOCs is commonly observed while their release shows cell line restricted patterns, whose underlying causes are unknown. The consumption of certain VOCs is commonly observed while their release shows cell line restricted patterns, whose underlying causes are unknown.

RAGE was analyzed by 2DE, MS and Western blotting using lung tissues from non smokers, smokers, patients with IPF, COPD and α-antitrypsin deficiency (AAT) and by ELISA. sRAGE was analyzed by ELISA.

RAGE was analyzed by ELISA. sRAGE was analyzed by ELISA. sRAGE was significantly lower (p = 0.007) in COPD patients (median 52 pg/mL, interquartile range 484 to 1076 pg/mL) than in controls (median 869 pg/mL, interquartile range 601 to 1240 pg/mL), and was correlated with his severity of emphysema (r = 0.26). The level of sRAGE was not significantly different between cases and controls.

RESULTS:

Analysis of volatile organic compounds (VOCs) in the headspace of NCI-H1666, which was originally derived from a bronchoalveolar carcinoma following detachment by trypsinization were incubated in a sealed fermenter for 21 hours. 200 ml of headspace from the cell cultures were sampled, diluted with dry, highly purified air and preconcentrated by adsorption on three different solid sorbents with increasing adsorption strength. VOCs were analyzed by thermal desorption gas chromatography mass spectrometry (TD-GC-MS). In contrast to our previous studies experiments with NCI-H1666, which was originally derived from a bronchoalveolar carcinoma following detachment by trypsinization were incubated in a sealed fermenter for 21 hours. 200 ml of headspace from the cell cultures were sampled, diluted with dry, highly purified air and preconcentrated by adsorption on three different solid sorbents with increasing adsorption strength. VOCs were analyzed by thermal desorption gas chromatography mass spectrometry (TD-GC-MS).

EXPERIMENTAL DESIGN:

VOCs were analyzed by TD-GC-MS. In contrast to our previous studies experiments with NCI-H1666, which was originally derived from a bronchoalveolar carcinoma following detachment by trypsinization were incubated in a sealed fermenter for 21 hours. 200 ml of headspace from the cell cultures were sampled, diluted with dry, highly purified air and preconcentrated by adsorption on three different solid sorbents with increasing adsorption strength. VOCs were analyzed by thermal desorption gas chromatography mass spectrometry (TD-GC-MS). In contrast to our previous studies experiments with NCI-H1666, which was originally derived from a bronchoalveolar carcinoma following detachment by trypsinization were incubated in a sealed fermenter for 21 hours. 200 ml of headspace from the cell cultures were sampled, diluted with dry, highly purified air and preconcentrated by adsorption on three different solid sorbents with increasing adsorption strength. VOCs were analyzed by thermal desorption gas chromatography mass spectrometry (TD-GC-MS). In contrast to our previous studies experiments with NCI-H1666, which was originally derived from a bronchoalveolar carcinoma following detachment by trypsinization were incubated in a sealed fermenter for 21 hours. 200 ml of headspace from the cell cultures were sampled, diluted with dry, highly purified air and preconcentrated by adsorption on three different solid sorbents with increasing adsorption strength. VOCs were analyzed by thermal desorption gas chromatography mass spectrometry (TD-GC-MS).

EMPIRICAL STUDIES:

RAGE and cRAGE, but no unequivocal release of VOCs was observed. Together with our previously published work these data indicate that the consumption of certain VOCs is commonly observed while their release shows cell line restricted patterns, whose underlying causes are unknown. The consumption of certain VOCs is commonly observed while their release shows cell line restricted patterns, whose underlying causes are unknown.
In COPD lungs, evidence of involvement of specific RAGE variants also in this disease.

Advanced glycation end products and its receptor (RAGE) are increased in patients with COPD.

Advanced glycation end products (AGEs) are the products of nonenzymatic glycation and oxidation of proteins and lipids. Formation of AGEs is increased in response to hyperglycaemia, reactive oxygen species and ageing. AGEs are proinflammatory and can modify the extracellular matrix. RAGE (Receptor for Advanced Glycation End Products) mediates some of the effects of AGEs.

METHODS: Formalin-fixed lung tissue from patients who had lobectomy for bronchial carcinoma was used to investigate the presence of AGEs and RAGE. Subjects were divided into those with COPD and controls. Immunostaining for AGEs and RAGE was performed and the intensity of staining measured.

RESULTS: Subjects with COPD and controls were similar in age and smoking history but FEV(1)% predicted was lower for COPD than controls. Intensity of staining for AGEs was greater in the airways (p = 0.025) and alveolar walls (p = 0.004) in COPD. Intensity of staining for RAGE was also significantly increased in alveolar walls (p = 0.03) but not the airways. SUV(1)% predicted was correlated with the intensity of staining for AGEs in the airways and alveoli.

CONCLUSIONS: The increased staining for both AGEs and RAGE in COPD lung raises the possibility that the RAGE-AGEs interaction may have a role in the pathogenesis of COPD.

Diesel particulate matter induces receptor for advanced glycation end products (RAGE) expression in pulmonary epithelial cells, and RAGE signaling influences NFκB-mediated inflammation.

BACKGROUND: Receptors for advanced glycation end-products (RAGE) are cell-surface receptors expressed by alveolar type I (ATI) epithelial cells and are implicated in mechanisms of alveolar development and sustained pulmonary inflammation.

OBJECTIVES: In the present study, we tested the hypothesis that diesel particulate matter (DPM) upregulates RAGE in rat ATI-like R3/1 cells and human primary small airway epithelial cells (SAECs), leading to an inflammatory response.

METHODS AND RESULTS: Using real-time reverse transcriptase polymerase chain reaction and immunoblotting, we found that RAGE mRNA and protein are upregulated in cells exposed to DPM for 2 hr. Use of a luciferase reporter containing nuclear factor-κB (NFκB) response elements revealed decreased NFκB activation in cells transfected with small interfering RNA (siRNA) for RAGE (siRAGE) before DPM exposure compared with cells transfected with scrambled control siRNA (siControl). In addition, immunostaining revealed diminished nuclear translocation of NFκB in DPM-exposed cells transfected with siRAGE compared with cells transfected with siControl before DPM stimulation. Enzyme-linked immunosorbent assay demonstrated that DPM induced secretion of monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8), two cytokines induced by NFκB and associated with leukocyte chemotaxis during an inflammatory response. Incorporating siRAGE was sufficient to significantly decrease DPM-induced MCP-1 and IL-8 secretion compared with cells transfected with siControl.

CONCLUSIONS: These data offer novel insights into potential mechanisms whereby RAGE influences pulmonary inflammatory responses initiated by DPM exposure. Further research may demonstrate that molecules involved in RAGE signaling are potential targets in lessening the degree of particulate matter-induced exacerbations of inflammatory lung disease.
Expression of high-mobility group box 1 and of receptor for advanced glycation end products in chronic obstructive pulmonary disease.

OBJECTIVES: To determine whether HMGB1 is augmented in COPD and is associated with IL-1β and RAGE.

METHODS: HMGB1 was assessed in the bronchoalveolar lavage (BAL) of 20 never-smokers, 20 smokers, and 30 smokers with COPD and it was correlated with inflammatory and clinical parameters. In parallel, HMGB1 and RAGE immunolocalization was determined in bronchial and lung tissues. Last, binding of HMGB1 to IL-1β was examined.

RESULTS: BAL levels of HMGB1 were higher in smokers with COPD than in smokers and never smokers (P < 0.0001 for both comparisons), and similar differences were observed in epithelial cells and alveolar macrophages. BAL HMGB1 correlated positively with IL-1β (r(s) = 0.438; P = 0.0006) and negatively with FEV₁ (r(s) = -0.570; P < 0.0001) and transfer factor of the lung for carbon monoxide (r(s) = -0.382; P = 0.0026). HMGB1 IL-1β complexes were found in BAL supernatant and alveolar macrophages from smokers and patients with COPD, as well as in the human macrophage cell line, THP-1, where they enhanced the synthesis of tumor necrosis factor-α.

RAGE was overexpressed in the airway epithelium and smooth muscle of patients with COPD and it colocalized with HMGB1.

CONCLUSIONS: Elevated HMGB1 expression in COPD airways may sustain inflammation and remodeling through its interaction with IL-1β and RAGE.
Noninvasive detection of lung cancer by analysis of exhaled breath.

**BACKGROUND:**
Lung cancer is one of the leading causes of death in Europe and the western world. At present, diagnosis of lung cancer very often happens late in the course of the disease since inexpensive, non-invasive and sufficiently sensitive and specific screening methods are not available. Even though the CT diagnostic methods are good, it must be assured that "screening benefit outweighs risk, across all individuals screened, not only those with lung cancer". An early non-invasive diagnosis of lung cancer would improve prognosis and enlarge treatment options. Analysis of exhaled breath would be an ideal diagnostic method, since it is non-invasive and totally painless.

**METHODS:**
Exhaled breath and indoor air samples were analyzed using proton transfer reaction mass spectrometry (PTR-MS) and solid phase microextraction with subsequent gas chromatography mass spectrometry (SPME-GCMS). For the PTR-MS measurements, 220 lung cancer patients and 441 healthy volunteers were recruited. For the GCMS measurements, we collected samples from 65 lung cancer patients and 31 healthy volunteers. Lung cancer patients were in different disease stages and under treatment with different regimes. Mixed exspiratory and indoor air samples were collected in Tedlar bags, and either analyzed directly by PTR-MS or transferred to glass vials and analyzed by gas chromatography mass spectrometry (GCMS). Only those measurements of compounds were considered, which showed at least a 15% higher concentration in exhaled breath than in indoor air. Compounds related to smoking behavior such as acetonitrile and benzene were not used to differentiate between lung cancer patients and healthy volunteers.

**RESULTS:**
Isoprene, acetone and methanol are compounds appearing in everybody's exhaled breath. These three main compounds of exhaled breath show slightly lower concentrations in lung cancer patients as compared to healthy volunteers (p < 0.01 for isoprene and acetone, p = 0.011 for methanol; PTR-MS measurements). A comparison of the GCMS results of 65 lung cancer patients with those of 31 healthy volunteers revealed more than 50 compounds, each with a significative difference in concentration for the two groups. Sensitivity for detection of lung cancer patients based on presence of (one of) 4 different compounds not arising in exhaled breath of healthy volunteers was 52% with a specificity of 100%. Using 15 (or 21) different compounds for distinction, sensitivity was 71% (80%) with a specificity of 100%. Potential marker compounds are alcohols, aldehydes, ketones and hydrocarbons.

**CONCLUSION:**
GCMS-SPME is a relatively insensitive method. Hence compounds not appearing in exhaled breath of healthy volunteers may be below the limit of detection (LOD). PTR-MS, on the other hand, does not need preconcentration and gives much more reliable quantitative results, than GCMS-SPME. The shortcoming of PTR-MS is that it cannot identify compounds with certainty, hence SPME-GCMS and PTR-MS complement each other, each method having its particular advantages and disadvantages. Exhaled breath analysis is promising to become a future non-invasive lung cancer screening method. In order to proceed towards this goal, precise identification of compounds observed in exhaled breath of lung cancer patients is necessary. Comparison with compounds released from lung cancer cell cultures, and additional information on exhaled breath composition in other cancer forms will be important.

**PubMed Identifier:** 19788722

**Publication:** Ager E, Agar C, Pienz M, Klieber M, Schwarz K, Turner M, Turner T, Höflisch P, Holzer W, Miehlke M, Weiss W, Lukas P, Jamnig H, Hackl M, Ligor T, Haidenberger A, Buszewski B, Miekisch W, Amann A. 

**PMID:** 19788722

**PMCID:** PMC2761408

**PMID:** 19788722
Changes in weather and the effects on pediatric asthma exacerbations.

BACKGROUND: Pediatric asthma exacerbations may correlate with changes in weather, yet this relationship is not well defined.

OBJECTIVE: To determine the effects of fluctuations in climatic factors (temperature, humidity, and barometric pressure) on pediatric asthma exacerbations.

METHODS: A retrospective study was performed at 1 large urban hospital during a 2-year period (January 1, 2004, to December 31, 2005). Children presenting to the emergency department (ED) for an asthma exacerbation were included. Data on climactic factors, pollutants, and allergens were collected daily. The relationship of daily (intraday) or between day (interday) changes in climatic factors and asthma ED visits was evaluated using time series analysis, controlling for seasonality, air pollution, and allergen exposure. The effects of climatic factors were evaluated in the day of admission (T=0) and up to 5 days before admission (T-5 through T-1).

RESULTS: There were 25,401 asthma ED visits. A 10% intraday increase in humidity on day T-1 or T-2 was associated with approximately 1 additional ED visit for asthma (P < .001 and P = .01, respectively). Interday changes in humidity from day T-3 to T-2 were also associated with more ED visits (P < .001). Interday changes in temperature from T-1 to T = 0 increased ED visits, with a 10 degrees F increase being associated with 1.8 additional visits (P = .006). No association was found with changes in barometric pressure.

CONCLUSION: Fluctuations in humidity and temperature, but not barometric pressure, appear to influence ED visits for pediatric asthma. The additional ED visits occur 1 to 2 days after the fluctuation.
Exhaled breath analysis in lung cancer

Determination of volatile organic compounds in exhaled breath of patients with lung cancer using solid phase microextraction and gas chromatography mass spectrometry.

BACKGROUND: Analysis of exhaled breath is a promising diagnostic method. Sampling of exhaled breath is non-invasive and can be performed as often as considered desirable. There are indications that the concentration and presence of certain volatile compounds in exhaled breath differ from concentrations in healthy volunteers. This might lead to a future diagnostic test for lung cancer.

METHODS: Exhaled breath samples from 65 patients with different stages of lung cancer and undergoing different treatment regimes were analysed. Mixed expiratory and indoor air samples were collected. Solid phase microextraction (SPME) with carboxen/polydimethylsiloxane (CAR/PDMS) sorbent was applied. Compounds were analysed by means of gas chromatography (GC) and mass spectrometry (MS).

RESULTS: The method we used allowed identification with the spectral library of 103 compounds showing at least 15% higher concentration in exhaled breath than in inhaled air. Among those 103 compounds, 84 were confirmed by determination of the retention time using standards based on the respective pure compound. Approximately, one third of the compounds detected were hydrocarbons. We found aromatic hydrocarbons, alcohols, aldehydes, ketones, esters, ethers, sulfur compounds, nitrogen-containing compounds and halogenated compounds. Acetonitrile and benzene were two of 10 compounds which correlated with smoking behaviour. A comparison of results from cancer patients with those of 31 healthy volunteers revealed differences in the concentration and presence of certain compounds. The sensitivity for detection of lung cancer patients based on eight different compounds not seen in exhaled breath of healthy volunteers was 51% and the specificity was 100%. These eight potential markers for detection of lung cancer are 1-propanol, 2-butanone, 3-butyn-2-ol, benzaldehyde, 2-methyl pentane, 3-methyl pentane, n-pentane and n-hexane.

CONCLUSIONS: SPME is a relatively insensitive method and compounds not observed in exhaled breath may be present at a concentration lower than LOD. The main achievement of the present work is the validated identification of compounds observed in exhaled breath of lung cancer patients. This identification is indispensable for future work on the biochemical sources of these compounds and their metabolic pathways.
Total serum IgE levels are associated with ambient ozone concentration in asthmatic adults.

METHODS:
The present study relates to the 369 asthmatic adults from the French Epidemiological study on Genetics and Environment of Asthma (EGEA), with availability of data on both total serum IgE measurements and air pollution concentrations. Five-statistical models were performed to assess individual outdoor air pollution exposure. Geo-statistical models were performed on 4 x 4 km grids to assess individual outdoor air pollution exposure. Annual outdoor concentrations of ozone (O_3), nitrogen dioxide (NO_2), sulphur dioxide (SO_2), and particular matter smaller than 10 microm size (PM_10), and concentrations of summer ozone were assigned to subject’s home address.

RESULTS:
The geometric mean of total IgE was 161 IU/ml and the average of O_3 exposure was 44.9 +/− 9.5 microg/m_3. Ozone concentrations were positively related to total IgE levels and an increase of 10 microg/m_3 of O_3 resulted in an increase of 20.4% (95% CI = 3.0 - 40.7) in total IgE levels. Adjustment for age, gender, smoking habits and previous life in the countryside did not change the results, and an increase of 19.1% (2.4 - 38.6) in total IgE was observed with O_3. Negative associations observed between NO_2 and total IgE levels disappeared after including O_3 in the models. Neither SO_2 nor PM_10 were correlated with total IgE levels.

CONCLUSIONS:
Results suggest that O_3 or related ambient pollutants may up-regulate total IgE levels among asthmatic adults.

Air pollution and asthma severity in adults.

BACKGROUND/OBJECTIVES:
There is evidence that exposure to air pollution affects asthma, but the effect of air pollution on asthma severity is less well documented. The aim was to assess whether asthma severity was associated with outdoor air pollution concentrations in adults.

METHODS:
Asthma severity over the past 12 months was assessed in two complementary ways among 328 adult asthmatics from the French Epidemiological study on the Genetics and Environment of Asthma (EGEA) examined between 1991 and 1995. The four-class severity score integrated clinical events and type of treatment. The five-level asthma score is based only on the occurrence of symptoms. Nitrogen dioxide (NO_2), sulphur dioxide (SO_2) and ozone (O_3) concentrations were assigned to each residence using two different methods. The first was based on the closest monitor data from 1991 to 1995. The second consisted of spatial models that used geostatistical interpolations and then assigned air pollutants to the geo-coded residences (1998).

RESULTS:
Higher asthma severity score was significantly related to the 8-hour average of ozone during April - September (O_3-8 h) and the number of days (O_3-days) with 8-hour ozone averages above 110 microg.m_3 (for a 36-day increase, equivalent to the interquartile range, in O_3-days, odds ratio 2.22 (95% confidence interval 1.61 to 3.07) for one class difference in score). Adjustment for age, sex, smoking habits, occupational exposure, and educational level did not alter results. Asthma severity was unrelated to NO_2. Both exposure assessment methods and severity scores resulted in very similar findings. SO_2 correlated with severity but reached statistical significance only for the model-based assignment of exposure.

CONCLUSIONS:
The observed associations between asthma severity and air pollution are probably due to ozone.
Pollution, in particular O\(_3\), support the hypothesis that air pollution at levels far below current standards increases asthma severity.

Immortalization of human alveolar epithelial cells to investigate nanoparticle uptake.

Primary human alveolar type 2 (AT2) cells, immortalized by transduction with the catalytic subunit of telomerase and simian virus 40 large tumor antigen. Characterization by immunochemical and morphologic methods demonstrated an AT2-like cell phenotype. Unlike primary AT2 cells, immortalized cells no longer expressed alkaline phosphatase, pro-surfactant protein C, and thyroid transcription factor-1, but expressed increased caveolin-1 and receptor for advanced glycation end products (RAGE). Live cell imaging using scanning ion conductance microscopy showed that the cuboidal primary AT2 cells were approximately 15 microm and enriched with surface microvilli, while the immortal AT1 cells were attenuated more than 40 microm, resembling these cells in vivo. Transmission electron microscopy highlighted the attenuated morphology and showed endosomal vesicles in some immortal AT1 cells (but not primary AT2 cells) as found in vivo. Particulate air pollution exacerbates cardiopulmonary disease.

We hypothesized differential uptake of nanoparticles by AT1 and AT2 cells, depending on particle size and surface charge. Uptake of 50-nm and 1-microm fluorescent latex particles was investigated using confocal microscopy and scanning surface confocal microscopy of live cells. Fewer than 10% of primary AT2 cells internalized particles. In contrast, 75% immortal AT1 cells internalized negatively charged particles, while less than 55% of these cells internalized positively charged particles; charge, rather than size, mattered. The process was rapid: one-third of the total cell-associated negatively charged 50-nm particle fluorescence measured at 24 hours was internalized during the first hour. AT1 cells could be important in translocation of particles from the lung into the circulation.
OBJECTIVES: This study examined prospectively (1971-1988) the relationship between anger-coping responses, gender, and mortality (N = 120) in a representative sample of men (N = 324) and women (N = 372), aged 30 to 69, from the Tecumseh Community Health Study.

METHODS: Anger-coping was measured by responses to hypothetical unfair anger-provoking situations. Cox proportional hazard regressions were used adjusted for seven health risk factors (age, smoking, relative weight, systolic blood pressure (SBP), bronchial problems, FEV1, and cardiovascular (CV) risk).

RESULTS: Men's suppressed anger interacted significantly with SBP and also with bronchial problems to predict both all-cause and CV mortality. Women showed direct relationships between suppressed anger and early mortality (all-cause, CV, and cancer). Women also showed an interaction of spouse-suppressed anger and SBP for all-cause and CV mortality. Data suggest men who expressed their anger died earlier of cancer (N = 16 deaths).

CONCLUSIONS: Suppressed anger at the time of an unjust attack may become chronic resentment (intermittent rage or hatred) about which little is known and requires research. The design for future research should experimentally measure both suppressed anger-coping responses (after an unfair attack) and morbidity (eg, blood pressure, bronchitis, immune disorder, etc.) to predict prospectively to earlier mortality.

Harburg E, Atkins M, Kaciroti N, Gleiberman L, Schork MA. Psychosom Med. 2003 Jul-Aug;65(4):588-97.

PMID:12883109 pubmed/12883109

Harburg E, Atkins M, Kaciroti N, Gleiberman L, Schork MA. Psychosom Med. 2003 Jul-Aug;65(4):588-97.

PMID:12883109 pubmed/12883109

Expression/suppression of anger-coping responses and types of mortality in a 17-year follow-up study of the Tecumseh Community Health Study, 1971-1988

CONCLUSIONS: The increased incidence of lung cancer (from 13% in 1950 to 20% in 1985) in both smokers and non-smokers suggests that lung cancer may have an environmental etiology other than smoking. To explore this possibility, we compared the patterns of gene expression in paired samples of tumor and normal lung tissue from 3 patients with a pathologic diagnosis of adenocarcinoma. Gene expression patterns of the paired tumor and normal tissue samples were performed by oligonucleotide microarray analysis of 12,000 known genes. The gene expression patterns of the paired tissue samples were characterized by 12 genes that were up-regulated > or = 2-fold in all 3 tumors and 6 genes that were down-regulated in all 3 tumors to < or = 0.20 times the baseline. These findings suggest that large scale transcriptional profiling of BC tumors may disclose a pattern of altered cellular expression in response to genetic changes, diseases, and environmental insult, such transcriptional profiling may aid in diagnosis and therapy.

Goodwin LO, Mason JM, Hopley S. Arch Pathol Lab Med. 2001 Dec;125(12):1576-84.

PMID:11688848 pubmed/11688848

Goodwin LO, Mason JM, Hopley S. Arch Pathol Lab Med. 2001 Dec;125(12):1576-84.

PMID:11688848 pubmed/11688848

Gene expression patterns of paired bronchioloalveolar carcinoma and benign lung tissue.
Autoantibodies have been described in human cancer patients as well as in animal models of malignancy. The extracellular matrix and especially basement membranes act as barriers for tumor cell invasion. Collagen, particularly types I, III, and IV, are major constituents of the extracellular matrix. We tested the hypothesis that cigarette smoke (CS) induces RAGE expression, and that autoantibodies to fibrillar collagen antigens are present in lung cancer. The pack-year smoking history was available in 133 patients; within 1 month of the initiation of therapy, serum levels of antibodies binding fibrillar collagen types I, III, and IV were significantly higher in CS smokers than in controls (62.4% of patients positive for one or more antifibrillar antibodies). Antibodies binding collagen antigens were not different between patients and control sera in the lung cancer patients. The level of serum antibodies binding collagen antigens increased significantly between baseline and 2 years of smoking only contributed to the variance in the level of serum antibody binding types IV and V. Lower levels of antibody binding type IV and higher levels of antibody binding type V were associated with small cell carcinoma.

We hypothesise that CS can induce RAGE expression, which mediates the inflammatory response in BEAS 2B cells. Further experiments are being conducted to explore the effect of CS on other inflammatory gene expression and to investigate the role of RAGE in modulating CS-induced inflammatory response in BEAS 2B cells.

Clinical studies show that smokers with or without COPD have anti-collagen antibodies as a pattern of immune recognition. The presence of these immune responses is thought to reflect the degree of disease processes including the degree of airflow obstruction. It is increasingly recognised that the innate immune pattern of chronic airway disease is the cell surface receptor for advanced glycation end products (RAGE). RAGE recently came to attention in chronic airway disease as a receptor that has key involvement in the chronic airway disease process. Autoantibodies to fibrillar collagen antigens are present frequently in lung cancer patients. Serum levels of antifibrillar antibodies contribute to the variance of progression free survival days, survival days, and the duration of favorable response to treatment. The pack-year smoking history was available in 133 patients; within 1 month of the initiation of therapy, serum levels of antibodies binding fibrillar collagen types I, III, and IV were significantly higher in CS smokers than in controls (62.4% of patients positive for one or more antifibrillar antibodies). Antibodies binding collagen antigens were not different between patients and control sera in the lung cancer patients. The level of serum antibodies binding collagen antigens increased significantly between baseline and 2 years of smoking only contributed to the variance in the level of serum antibody binding types IV and V. Lower levels of antibody binding type IV and higher levels of antibody binding type V were associated with small cell carcinoma.

We hypothesise that CS can induce RAGE expression, which mediates the inflammatory response in BEAS 2B cells. Further experiments are being conducted to explore the effect of CS on other inflammatory gene expression and to investigate the role of RAGE in modulating CS-induced inflammatory response in BEAS 2B cells.
Background. Idiopathic interstitial pneumonias (IIPs) are a group of heterogeneous, chronic, fibrotic diseases characterized by progressive scarring of the lung structure. Since lung function is a key determinant of survival, we measured that the transcriptional profile in IIP lung tissue would be associated with measures of lung function, and autoimmune, angiogenic, and fibrotic pathways. Results: Using gene expression profiling of 167 lung tissue specimens with IIP diagnosis and 50 control lungs, we identified genes whose expression is significantly associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as continuous (when modeled as categorical variables while adjusting for smoking status and IIP subtype; false discovery rate (FDR) approach was used to correct for multiple comparisons. This analysis identified 58 transcripts that are associated with mild vs severe disease (categorical analysis), and could enhance prognostic approaches to IIPs. Results: Using gene expression profiling of 167 lung tissue specimens with IIP diagnosis and 50 control lungs, we identified genes whose expression is significantly associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as continuous (when modeled as categorical variables while adjusting for smoking status and IIP subtype; false discovery rate (FDR) approach was used to correct for multiple comparisons. This analysis identified 58 transcripts that are associated with mild vs severe disease (categorical analysis), and could enhance prognostic approaches to IIPs.

Conclusion: In COPD, AGEs accumulate differentially in body compartments. Since lung function is a key determinant of survival, we measured that the transcriptional profile in COPD patients would be associated with measures of lung function, and autoimmune, angiogenic, and fibrotic pathways. Results: Using gene expression profiling of 167 lung tissue specimens with COPD diagnosis and 50 control lungs, we identified genes whose expression is significantly associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as continuous (when modeled as categorical variables while adjusting for smoking status and IIP subtype; false discovery rate (FDR) approach was used to correct for multiple comparisons. This analysis identified 58 transcripts that are associated with mild vs severe disease (categorical analysis), and could enhance prognostic approaches to IIPs. Results: Using gene expression profiling of 167 lung tissue specimens with COPD diagnosis and 50 control lungs, we identified genes whose expression is significantly associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as continuous (when modeled as categorical variables while adjusting for smoking status and IIP subtype; false discovery rate (FDR) approach was used to correct for multiple comparisons. This analysis identified 58 transcripts that are associated with mild vs severe disease (categorical analysis), and could enhance prognostic approaches to IIPs. Results: Using gene expression profiling of 167 lung tissue specimens with COPD diagnosis and 50 control lungs, we identified genes whose expression is significantly associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as continuous (when modeled as categorical variables while adjusting for smoking status and IIP subtype; false discovery rate (FDR) approach was used to correct for multiple comparisons. This analysis identified 58 transcripts that are associated with mild vs severe disease (categorical analysis), and could enhance prognostic approaches to IIPs. Results: Using gene expression profiling of 167 lung tissue specimens with COPD diagnosis and 50 control lungs, we identified genes whose expression is significantly associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as continuous (when modeled as categorical variables while adjusting for smoking status and IIP subtype; false discovery rate (FDR) approach was used to correct for multiple comparisons. This analysis identified 58 transcripts that are associated with mild vs severe disease (categorical analysis), and could enhance prognostic approaches to IIPs.

Conclusion: In COPD, AGEs accumulate differentially in body compartments. Since lung function is a key determinant of survival, we measured that the transcriptional profile in COPD patients would be associated with measures of lung function, and autoimmune, angiogenic, and fibrotic pathways. Results: Using gene expression profiling of 167 lung tissue specimens with COPD diagnosis and 50 control lungs, we identified genes whose expression is significantly associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as continuous (when modeled as categorical variables while adjusting for smoking status and IIP subtype; false discovery rate (FDR) approach was used to correct for multiple comparisons. This analysis identified 58 transcripts that are associated with mild vs severe disease (categorical analysis), and could enhance prognostic approaches to IIPs. Results: Using gene expression profiling of 167 lung tissue specimens with COPD diagnosis and 50 control lungs, we identified genes whose expression is significantly associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as continuous (when modeled as categorical variables while adjusting for smoking status and IIP subtype; false discovery rate (FDR) approach was used to correct for multiple comparisons. This analysis identified 58 transcripts that are associated with mild vs severe disease (categorical analysis), and could enhance prognostic approaches to IIPs. Results: Using gene expression profiling of 167 lung tissue specimens with COPD diagnosis and 50 control lungs, we identified genes whose expression is significantly associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as continuous (when modeled as categorical variables while adjusting for smoking status and IIP subtype; false discovery rate (FDR) approach was used to correct for multiple comparisons. This analysis identified 58 transcripts that are associated with mild vs severe disease (categorical analysis), and could enhance prognostic approaches to IIPs. Results: Using gene expression profiling of 167 lung tissue specimens with COPD diagnosis and 50 control lungs, we identified genes whose expression is significantly associated with changes in lung function (% predicted FVC and % predicted DLCO) modeled as continuous (when modeled as categorical variables while adjusting for smoking status and IIP subtype; false discovery rate (FDR) approach was used to correct for multiple comparisons. This analysis identified 58 transcripts that are associated with mild vs severe disease (categorical analysis), and could enhance prognostic approaches to IIPs.
Background Chronic obstructive pulmonary disease (COPD) is associated with systemic inflammatory consequences. Receptor for advanced glycation end products (RAGE) acts as an important progression factor amplifying the immune and inflammatory response in several pathological conditions. The soluble form of RAGE (sRAGE) acts as a decoy for the receptor ligands and is thus thought to protect against excessive inflammation. Conflicting results exist about sRAGE value in stable and exacerbating COPD. Objective To assess sRAGE to plasma ratio of sRAGE in stable COPD patients. Subjects and methods: The study included 44 adult patients of both sexes who were presented to Alexandria Main University Hospital between March and July 2015. Patients were categorized into three groups: 15 stable COPD patients (Group I), 15 smokers without COPD (Group II), and 14 healthy non-smokers (Group III).Measurement of sRAGE level in induced sputum and plasma was performed using ELISA technique. Results The study included 44 adult patients of both sexes whose median ages were 50, 42 and 35 years in Groups I, II and III respectively (P = 0.05). Median FEV1% predicted were 50, 65 and 80% in Groups I, II and III respectively (P = 0.001). No statistical significant difference was found among all groups regarding sRAGE level in induced sputum. Regarding plasma sRAGE level, statistical significant difference was found among all groups (P = 0.001).Conclusion sRAGE level in induced sputum, plasma or plasma ratio is not significantly different between stable COPD patients, smokers and healthy controls. These findings can be considered as an important tool in the treatment of COPD. Accepted for publication: 25 May 2016. Date of Publication: 01 Jul 2016...
Hypothesis: Chronic obstructive pulmonary disease (COPD) is defined by the presence of airflow limitation on spirometry, yet subjects with COPD can have marked differences in computed tomography imaging. These differences may be driven by genetic factors. We hypothesized that a genome-wide association study (GWAS) of quantitative imaging would identify loci not previously identified in analyses of COPD on spirometry. In addition, we sought to determine whether previously described genome-wide significant COPD and spirometric loci were associated with emphysema or airway phenotypes.

Methods: We performed a GWAS on two quantitative emphysema and two quantitative airway imaging phenotypes in five COPD cohorts (non-Hispanic white and African American in COPDGene, and participants in the National Emphysema Treatment Trial, NETT, and Evaluation of COPD Longitudinally to Identify Predictive Surrogates Endpoints, ECLIPSE). We also examined specific loci reported as genomewide significant for spirometric phenotypes related to airflow limitation or COPD. Measurements and Main Results: The total sample size across all cohorts was 12,031, of whom 9,338 were from COPDGene. We identified five loci associated with emphysema-related phenotypes, one with airway-related phenotypes, and two with gas trapping. These loci included previously reported associations, including the HHIP, 15q25, and AGER loci, as well as novel associations near SERPINA10 and DLC1. All previously reported COPD and a significant number of spirometric GWAS loci were at least nominally (P < 0.05) associated with either emphysema or airway phenotypes. Conclusions: Genome-wide analysis may identify novel loci for quantitative imaging characteristics that may be used in the development of lung repair therapies.
Receptor for advanced glycation end products (RAGE), a multiligand receptor in the innate immune system, plays a crucial role in the regulation of lung fluid balance. We quantified soluble RAGE (sRAGE) in a diverse, non-selected, and advanced glycation end products (AGE)-exposed cohort of patients with varying stages of lung cancer to clarify the biological role of the RAGE gene, and to aid diagnosis and predict the prognosis for lung cancer patients. Additionally, advanced glycation end products (RAGE) is receiving increasing attention as a relevant molecule due to its involvement in multiple pathological effects mediated through RAGE. In this review, we describe the association between circulating RAGE and RAGE ligands in human diseases, the role of RAGE in the progression and metastasis of lung cancer, and the regulation of lung fluid balance. We quantified soluble RAGE (sRAGE), the receptor for advanced glycation end products (RAGE), in lung cancer patients. The association between circulating sRAGE and RAGE ligands was analyzed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer. In a selected cohort of lung cancer patients, sRAGE levels were found to be significantly reduced in serum compared to controls. This finding was confirmed in a large meta-analysis involving nine eligible articles including 1,337 cancer patients and 1,205 healthy controls. Analysis of the data showed a significant heterogeneity (I2 = 56.5%, P = 0.056) explained by study design (WMD = 0.004), with heterogeneity and without publication bias. In subgroup analysis, the comparison between various histological subtypes and stages of lung cancer was performed with the aim to identify a biomarker and a potential therapeutic target for lung cancer.
The association of plasma biomarkers with quantified emphysema phenotypes. We measured plasma levels of the high mobility group protein B1 (HMGB1) and soluble RAGE (sRAGE) levels has not been clearly clarified. The aim of this study was to assess these issues. We performed a comprehensive biomarker panel, we sought to determine if the correlation between acute exacerbation and smoking history and FEV1\% pred. Levels of HMGB1 and sRAGE were the highest in the current smoker group, and significantly decreased in ex smoker group in both acute exacerbation and convalescence phase of COPD. However, their levels in never smoker group were slightly lower in acute exacerbation phase than in convalescence phase. On the other hand, HMGB1 and sRAGE level were dynamically changed between exacerbation and convalescence phase of COPD. HMGB1 and sRAGE were likely not only a potential marker in COPD exacerbation but also a therapeutic target for COPD treatment.

Changes of HMGB1 and sRAGE during the course of COPD exacerbation. Background: Acute exacerbation of chronic obstructive pulmonary disease is associated with increased airflow limitation and systemic inflammation. However, the correlation between acute exacerbation and inflammation is not completely clarified. The aim of this study was to assess these issues. Methods: A total of 44 COPD patients were recruited. Following a structured interview, plasma levels of HMGB1, sRAGE, C1q/C4 and serum level of high mobility group protein B1 (HMGB1) were measured in patients with acute exacerbation of COPD (AECOPD) during hospitalization and pre-discharge (convalescence). All patients were exhaled with spirometry in accordance of COPD. Results: There was a significant decline in plasma HMGB1 (P<0.01), sRAGE (P<0.001) and C1q/C4 (P<0.001) levels from acute exacerbation to convalescence phase of COPD. Changes of sRAGE was significantly correlated with changes of HMGB1 (P<0.04). COPD disease correlates with the ratio of HMGB1/sRAGE, but not gender, age, course of disease, smoking history and FEV1% pred. Levels of HMGB1 and sRAGE were the highest in the current smoker group, and significantly decreased in ex smoker group in both acute exacerbation and convalescence phase of COPD. However, their levels in never smoker group were slightly lower in acute exacerbation phase than in convalescence phase. On the other hand, HMGB1 and sRAGE level were dynamically changed between exacerbation and convalescence phase of COPD. HMGB1 and sRAGE were likely not only a potential marker in COPD exacerbation but also a therapeutic target for COPD treatment.

Regulatory status: The association of plasma biomarkers with quantified emphysema phenotypes.

The association of plasma biomarkers with quantified emphysema phenotypes. We measured plasma levels of the high mobility group protein B1 (HMGB1) and soluble RAGE (sRAGE) levels has not been clearly clarified. The aim of this study was to assess these issues. We performed a comprehensive biomarker panel, we sought to determine if the correlation between acute exacerbation and smoking history and FEV1\% pred. Levels of HMGB1 and sRAGE were the highest in the current smoker group, and significantly decreased in ex smoker group in both acute exacerbation and convalescence phase of COPD. However, their levels in never smoker group were slightly lower in acute exacerbation phase than in convalescence phase. On the other hand, HMGB1 and sRAGE level were dynamically changed between exacerbation and convalescence phase of COPD. HMGB1 and sRAGE were likely not only a potential marker in COPD exacerbation but also a therapeutic target for COPD treatment.

Changes of HMGB1 and sRAGE during the course of COPD exacerbation. Background: Acute exacerbation of chronic obstructive pulmonary disease is associated with increased airflow limitation and systemic inflammation. However, the correlation between acute exacerbation and inflammation is not completely clarified. The aim of this study was to assess these issues. Methods: A total of 44 COPD patients were recruited. Following a structured interview, plasma levels of HMGB1, sRAGE, C1q/C4 and serum level of high mobility group protein B1 (HMGB1) were measured in patients with acute exacerbation of COPD (AECOPD) during hospitalization and pre-discharge (convalescence). All patients were exhaled with spirometry in accordance of COPD. Results: There was a significant decline in plasma HMGB1 (P<0.01), sRAGE (P<0.001) and C1q/C4 (P<0.001) levels from acute exacerbation to convalescence phase of COPD. Changes of sRAGE was significantly correlated with changes of HMGB1 (P<0.04). COPD disease correlates with the ratio of HMGB1/sRAGE, but not gender, age, course of disease, smoking history and FEV1% pred. Levels of HMGB1 and sRAGE were the highest in the current smoker group, and significantly decreased in ex smoker group in both acute exacerbation and convalescence phase of COPD. However, their levels in never smoker group were slightly lower in acute exacerbation phase than in convalescence phase. On the other hand, HMGB1 and sRAGE level were dynamically changed between exacerbation and convalescence phase of COPD. HMGB1 and sRAGE were likely not only a potential marker in COPD exacerbation but also a therapeutic target for COPD treatment.
Bronze speaking crossclassification analysis demonstrated a benefit of adding a biomarker panel to clinical covariates for detecting patients, especially in chronic obstructive pulmonary disease and/or COPD. The findings, support a panel of biomarkers including sRAGE, CML and the SNP in CHF in patients with CHF+COPD and 0.001. COPD has been proven in Chinese Han population, nor have COPD or lung function. However, their association with COPD has been demonstrated in chronic heart failure. In this study on patients with CHF and COPD, and whether plasma sRAGE and CML levels are correlated with sRAGE, but not with CML, in the patient groups: CHF (P > 0.05) and CHF+COPD patients and controls. The SNP (rs3995090) in HTR4 was associated with forced expiratory volume in 1 s (FEV1%) predicted (β = -0.071, adjusted P = 0.009) in all subjects. Associations between five single nucleotide polymorphisms (SNP) in CHF were assessed. Associations between variants at five loci (TNS1, GSTCD, THSD4, AGER and HTR4) and chronic obstructive pulmonary disease (COPD) or lung function in a Chinese Han population.
Conclusions: Plasma levels of sRAGE and CML are increased in CHF, but not in COPD patients. The robust association between NT-proBNP, a diagnostic and prognostic marker in CHF, and NGAL concentrations might suggest a possible BNP pathway of amplification of inflammation via the AGE/RAGE system

Advanced glycation end products and its receptor (RAGE) are increased in patients with COPD. Advanced glycation end products (AGEs) are the products of nonenzymatic glycation and oxidation of proteins and lipids. Formation of AGEs is increased in response to hyperglycaemia, reactive oxygen species and ageing. AGEs are proinflammatory and can modify the extracellular matrix. RAGE (Receptor for Advanced Glycation End Products) mediates some of the effects of AGEs. Methods: Formalin-fixed lung tissue from patients who had undergone lobectomy for bronchial carcinoma was used to investigate the presence of AGEs and RAGE. Subjects were divided into those with COPD and controls. Immunostaining for AGEs and RAGE was performed and the intensity of staining measured. Results: Subjects with COPD and controls were similar in age and smoking history but FEV1% predicted was lower for COPD than controls. Intensity of staining for AGEs was greater in the airways (p = 0.025) and alveolar walls (p = 0.004) in COPD. Intensity of staining for RAGE was also significantly increased in alveolar walls (p = 0.03) but not the airways. FEV1% predicted was correlated with the intensity of staining for AGEs in the airways and alveoli. Conclusions: The increased staining for both AGEs and RAGE in COPD may raise the possibility that the RAGE-AGE interaction may have a role in the pathogenesis of COPD.