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| **Supplemental Table 5. Studies that met inclusion and exclusion criteria (n=19)** | | | | | | | | | | | | | | | | |
| **S #** |  | **Comment** | **pdfs** |  | **Title** | **Abstract** | **URL** | **Description** | **Details** | **Short Details** | **Resource** | **Type** | **Identifiers** | **Db** | **EntrezUID** | **Properties** |
| 1 | 1 |  | 1 | PM | Receptor for advanced glycation end-products and World Trade Center particulate induced lung function loss: A case-cohort study and murine model of acute particulate exposure. | World Trade Center-particulate matter(WTC-PM) exposure and metabolic-risk are associated with WTC-Lung Injury(WTC-LI). The receptor for advanced glycation end-products (RAGE) is most highly expressed in the lung, mediates metabolic risk, and single-nucleotide polymorphisms at the AGER-locus predict forced expiratory volume(FEV). Our objectives were to test the hypotheses that RAGE is a biomarker of WTC-LI in the FDNY-cohort and that loss of RAGE in a murine model would protect against acute PM-induced lung disease. We know from previous work that early intense exposure at the time of the WTC collapse was most predictive of WTC-LI therefore we utilized a murine model of intense acute PM-exposure to determine if loss of RAGE is protective and to identify signaling/cytokine intermediates. This study builds on a continuing effort to identify serum biomarkers that predict the development of WTC-LI. A case-cohort design was used to analyze a focused cohort of male never-smokers with normal pre-9/11 lung function. Odds of developing WTC-LI increased by 1.2, 1.8 and 1.0 in firefighters with soluble RAGE (sRAGE)≥97pg/mL, CRP≥2.4mg/L, and MMP-9≤397ng/mL, respectively, assessed in a multivariate logistic regression model (ROCAUC of 0.72). Wild type(WT) and RAGE-deficient(Ager-/-) mice were exposed to PM or PBS-control by oropharyngeal aspiration. Lung function, airway hyperreactivity, bronchoalveolar lavage, histology, transcription factors and plasma/BAL cytokines were quantified. WT-PM mice had decreased FEV and compliance, and increased airwayresistance and methacholine reactivity after 24-hours. Decreased IFN-γ and increased LPA were observed in WT-PM mice; similar findings have been reported for firefighters who eventually develop WTC-LI. In the murine model, lack of RAGE was protective from loss of lung function and airwayhyperreactivity and was associated with modulation of MAP kinases. We conclude that in a multivariate adjusted model increased sRAGE is associated with WTC-LI. In our murine model, absence of RAGEmitigated acute deleterious effects of PM and may be a biologically plausible mediator of PM-related lung disease. | /pubmed/28926576 | Caraher EJ, Kwon S, Haider SH, Crowley G, Lee A, Ebrahim M, Zhang L, Chen LC, Gordon T, Liu M, Prezant DJ, Schmidt AM, Nolan A. | PLoS One. 2017 Sep 19;12(9):e0184331. doi: 10.1371/journal.pone.0184331. eCollection 2017. | PLoS One. 2017 | PubMed | citation | PMID:28926576 | PMCID:PMC5604982 | pubmed | 28926576 | create date:2017/09/20 | first author:Caraher EJ |
| 2 | 1 | not looking at OAD | 1 | Smoking | A Pilot Study Linking Endothelial Injury in Lungs and Kidneys in Chronic Obstructive Pulmonary Disease. | RATIONALE: Patients with chronic obstructive pulmonary disease (COPD) frequently have albuminuria (indicative of renal endothelial cell injury) associated with hypoxemia.  OBJECTIVES: To determine whether (1) cigarette smoke (CS)-induced pulmonary and renal endothelial cell injury explains the association between albuminuria and COPD, (2) CS-induced albuminuria is linked to increases in the oxidative stress-advanced glycation end products (AGEs) receptor for AGEs (RAGE) pathway, and (3) enalapril (which has antioxidant properties) limits the progression of pulmonary and renal injury by reducing activation of the AGEs-RAGE pathway in endothelial cells in both organs.  METHODS: In 26 patients with COPD, 24 ever-smokers without COPD, 32 nonsmokers who underwent a renal biopsy or nephrectomy, and in CS-exposed mice, we assessed pathologic and ultrastructural renal lesions, and measured urinary albumin/creatinine ratios, tissue oxidative stress levels, and AGEs and RAGE levels in pulmonary and renal endothelial cells. The efficacy of enalapril on pulmonary and renal lesions was assessed in CS-exposed mice.  MEASUREMENTS AND MAIN RESULTS: Patients with COPD and/or CS-exposed mice had chronic renal injury, increased urinary albumin/creatinine ratios, and increased tissue oxidative stress and AGEs-RAGE levels in pulmonary and renal endothelial cells. Treating mice with enalapril attenuated CS-induced increases in urinary albumin/creatinine ratios, tissue oxidative stress levels, endothelial cell AGEs and RAGE levels, pulmonary and renal cell apoptosis, and the progression of chronic renal and pulmonary lesions.  CONCLUSIONS: Patients with COPD and/or CS-exposed mice have pulmonary and renal endothelial cell injury linked to increased endothelial cell AGEs and RAGE levels. Albuminuria could identify patients with COPD in whom angiotensin-converting enzyme inhibitor therapy improves renal and lung function by reducing endothelial injury. | /pubmed/28085500 | Polverino F, Laucho-Contreras ME, Petersen H, Bijol V, Sholl LM, Choi ME, Divo M, Pinto-Plata V, Chetta A, Tesfaigzi Y, Celli BR, Owen CA. | Am J Respir Crit Care Med. 2017 Jun 1;195(11):1464-1476. doi: 10.1164/rccm.201609-1765OC. | Am J Respir Crit Care Med. 2017 | PubMed | citation | PMID:28085500 | PMCID:PMC5470750 | pubmed | 28085500 | create date:2017/01/14 | first author:Polverino F |
| 3 | 1 | assoc of smoking and RAGE in paper | 1 | Smoking | The Ser82 RAGE Variant Affects Lung Function and Serum RAGE in Smokers and sRAGE Production In Vitro. | INTRODUCTION: Genome-Wide Association Studies have identified associations between lung function measures and Chronic Obstructive Pulmonary Disease (COPD) and chromosome region 6p21 containing the gene for the Advanced Glycation End Product Receptor (AGER, encoding RAGE). We aimed to (i) characterise RAGE expression in the lung, (ii) identify AGER transcripts, (iii) ascertain if SNP rs2070600 (Gly82Ser C/T) is associated with lung function and serum sRAGE levels and (iv) identify whether the Gly82Ser variant is functionally important in altering sRAGE levels in an airway epithelial cell model.  METHODS: Immunohistochemistry was used to identify RAGE protein expression in 26 human tissues and qPCR was used to quantify AGER mRNA in lung cells. Gene expression array data was used to identify AGER expression during lung development in 38 fetal lung samples. RNA-Seq was used to identify AGER transcripts in lung cells. sRAGE levels were assessed in cells and patient serum by ELISA. BEAS2B-R1 cells were transfected to overexpress RAGE protein with either the Gly82 or Ser82 variant and sRAGE levels identified.  RESULTS: Immunohistochemical assessment of 6 adult lung samples identified high RAGE expression in the alveoli of healthy adults and individuals with COPD. AGER/RAGE expression increased across developmental stages in human fetal lung at both the mRNA (38 samples) and protein levels (20 samples). Extensive AGER splicing was identified. The rs2070600T (Ser82) allele is associated with higher FEV1, FEV1/FVC and lower serum sRAGE levels in UK smokers. Using an airway epithelium model overexpressing the Gly82 or Ser82 variants we found that HMGB1 activation of the RAGE-Ser82 receptor results in lower sRAGE production.  CONCLUSIONS: This study provides new information regarding the expression profile and potential role of RAGE in the human lung and shows a functional role of the Gly82Ser variant. These findings advance our understanding of the potential mechanisms underlying COPD particularly for carriers of this AGER polymorphism. | /pubmed/27755550 | Miller S, Henry AP, Hodge E, Kheirallah AK, Billington CK, Rimington TL, Bhaker SK, Obeidat M, MelÃ©n E, Merid SK, Swan C, Gowland C, Nelson CP, Stewart CE, Bolton CE, Kilty I, Malarstig A, Parker SG, Moffatt MF, Wardlaw AJ, Hall IP, Sayers I. | PLoS One. 2016 Oct 18;11(10):e0164041. doi: 10.1371/journal.pone.0164041. eCollection 2016. | PLoS One. 2016 | PubMed | citation | PMID:27755550 | PMCID:PMC5068780 | pubmed | 27755550 | create date:2016/10/19 | first author:Miller S |
| 4 | 1 |  | 1 | PM | Associations of autophagy with lung diffusion capacity and oxygen saturation in severe COPD: effects of particulate air pollution. | Although traffic exposure has been associated with the development of COPD, the role of particulate matter <10 μm in aerodynamic diameter (PM10) in the pathogenesis of COPD is not yet fully understood. We assessed the 1-year effect of exposure to PM10 on the pathogenesis of COPD in a retrospective cohort study. We recruited 53 subjects with COPD stages III and IV and 15 healthy controls in a hospital in Taiwan. We estimated the 1-year annual mean levels of PM10 at all residential addresses of the cohort participants. Changes in PM10 for the 1-year averages in quintiles were related to diffusion capacity of the lung for carbon monoxide levels (r=-0.914, P=0.029), changes in the pulse oxygen saturation (ΔSaO2; r=-0.973, P=0.005), receptor for advanced glycation end-products (r=-0.881, P=0.048), interleukin-6 (r=0.986, P=0.002), ubiquitin (r=0.940, P=0.017), and beclin 1 (r=0.923, P=0.025) in COPD. Next, we observed that ubiquitin was correlated with ΔSaO2 (r=-0.374, P=0.019). Beclin 1 was associated with diffusion capacity of the lung for carbon monoxide (r=-0.362, P=0.028), ΔSaO2 (r=-0.354, P=0.032), and receptor for advanced glycation end-products (r=-0.471, P=0.004). Autophagy may be an important regulator of the PM10-related pathogenesis of COPD, which could cause deterioration in the lung diffusion capacity and oxygen saturation. | /pubmed/27468231 | Lee KY, Chiang LL, Ho SC, Liu WT, Chen TT, Feng PH, Su CL, Chuang KJ, Chang CC, Chuang HC. | Int J Chron Obstruct Pulmon Dis. 2016 Jul 11;11:1569-78. doi: 10.2147/COPD.S108993. eCollection 2016. | Int J Chron Obstruct Pulmon Dis. 2016 | PubMed | citation | PMID:27468231 | PMCID:PMC4946865 | pubmed | 27468231 | create date:2016/07/29 | first author:Lee KY |
| 5 | 1 | studies healthy smokers | 1 | Smoking | Advanced glycation endproducts and their receptor in different body compartments in COPD. | BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by chronic airway inflammation and emphysema, and is caused by exposure to noxious particles or gases, e.g. cigarette smoke. Smoking and oxidative stress lead to accelerated formation and accumulation of advanced glycation end products (AGEs), causing local tissue damage either directly or by binding the receptor for AGEs (RAGE). This study assessed 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.  METHODS: Healthy smoking and never-smoking controls (n = 191) and COPD patients (n = 97, GOLD stage I-IV) were included. Autofluorescence (SAF) was measured in the skin, AGEs (pentosidine, CML and CEL) and sRAGE in blood and sputum by ELISA, and in bronchial biopsies by immunohistochemistry. eQTL analysis was performed in bronchial biopsies.  RESULTS: COPD patients showed higher SAF values and lower plasma sRAGE levels compared to controls and these values associated with decreased lung function (p <0.001; adjusting for relevant covariates). Lower plasma sRAGE levels significantly and independently predicted higher SAF values (p < 0.001). One SNP (rs2071278) was identified within a region of 50 kB flanking the AGER gene, which was associated with the gene and protein expression levels of AGER and another SNP (rs2071278) which was associated with the accumulation of AGEs in the skin.  CONCLUSION: In COPD, 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 SAF levels supports the hypothesis that the protective mechanism of sRAGE as a decoy-receptor is impaired in COPD. | /pubmed/27117828 | Hoonhorst SJ, Lo Tam Loi AT, Pouwels SD, Faiz A, Telenga ED, van den Berge M, Koenderman L, Lammers JW, Boezen HM, van Oosterhout AJ, Lodewijk ME, Timens W, Postma DS, Ten Hacken NH. | Respir Res. 2016 Apr 26;17:46. doi: 10.1186/s12931-016-0363-2. | Respir Res. 2016 | PubMed | citation | PMID:27117828 | PMCID:PMC4847335 | pubmed | 27117828 | create date:2016/04/28 | first author:Hoonhorst SJ |
| 6 | 1 |  | 1 | Smoking | Traditional and emerging indicators of cardiovascular risk in chronic obstructive pulmonary disease. | With the increased cardiovascular (CV) morbidity and mortality in subjects with chronic obstructive pulmonary disease (COPD), there is a priority to identify those patients at increased risk of cardiovascular disease. Stable patients with COPD (n = 185) and controls with a smoking history (n = 106) underwent aortic pulse wave velocity (PWV), blood pressure (BP) and skin autofluorescence (AF) at clinical stability. Blood was sent for fasting lipids, soluble receptor for advanced glycation end products (sRAGE) and CV risk prediction scores were calculated. More patients (18%) had a self-reported history of CV disease than controls (8%), p = 0.02, whilst diabetes was similar (14% and 10%), p = 0.44. Mean (SD) skin AF was greater in patients: 3.1 (0.5) AU than controls 2.8 (0.6) AU, p < 0.001. Aortic 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 in well-defined subjects with and without COPD. Two non-invasive biomarkers associated with future CV burden: skin AF and aortic PWV are both significantly greater in patients with COPD compared to the controls. The traditional CV prediction scores used in the general population were not statistically different. We provide new data to suggest that alternative approaches for optimal CV risk detection should be employed in COPD management. | /pubmed/26965223 | John M, McKeever TM, Haddad MA, Hall IP, Sayers I, Cockcroft JR, Bolton CE. | Chron Respir Dis. 2016 Aug;13(3):247-55. doi: 10.1177/1479972316636995. Epub 2016 Mar 10. | Chron Respir Dis. 2016 | PubMed | citation | PMID:26965223 | PMCID:PMC5720186 | pubmed | 26965223 | create date:2016/03/12 | first author:John M |
| 7 | 1 | blood biomarkers in CT assessed emphysema (includes sRAGE), not assesses the exposure assoc OAD | 1 | Smoking | The association of plasma biomarkers with computed tomography-assessed emphysema phenotypes. | RATIONALE: Chronic obstructive pulmonary disease (COPD) is a phenotypically heterogeneous disease. In COPD, the presence of emphysema is associated with increased mortality and risk of lung cancer. High resolution computed tomography (HRCT) scans are useful in quantifying emphysema but are associated with radiation exposure and high incidence of false positive findings (i.e., nodules). Using a comprehensive biomarker panel, we sought to determine if there was a peripheral blood biomarker signature of emphysema.  METHODS: 114 plasma biomarkers were measured using a custom assay in 588 individuals enrolled in the COPDGene study. Quantitative emphysema measurements included percent low lung attenuation (%LAA) ≤ -950 HU, ≤ - 910 HU and mean lung attenuation at the 15th percentile on lung attenuation curve (LP15A). 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: Regression analysis identified multiple biomarkers associated with CT-assessed emphysema in COPDGene, including advanced glycosylation end-products receptor (AGER or RAGE, p < 0.001), intercellular adhesion molecule 1 (ICAM, p < 0.001), and chemokine ligand 20 (CCL20, p < 0.001). Validation in the TESRA cohort revealed significant associations with RAGE, ICAM1, and CCL20 with radiologic emphysema (p < 0.001 after meta-analysis). Other biomarkers that were associated with emphysema include CDH1, CDH 13 and SERPINA7, but were not available for validation in the TESRA study. Receiver operating characteristics analysis demonstrated a benefit of adding a biomarker panel to clinical covariates for detecting emphysema, especially in those without severe airflow limitation (AUC 0.85).  CONCLUSIONS: Our findings, suggest that a panel of blood biomarkers including sRAGE, ICAM1 and CCL20 may serve as a useful surrogate measure of emphysema, and when combined with clinical covariates, may be useful clinically in predicting the presence of emphysema compared to just using covariates alone, especially in those with less severe COPD. Ultimately biomarkers may shed light on disease pathogenesis, providing targets for new treatments. | /pubmed/25306249 | Carolan BJ, Hughes G, Morrow J, Hersh CP, O'Neal WK, Rennard S, Pillai SG, Belloni P, Cockayne DA, Comellas AP, Han M, Zemans RL, Kechris K, Bowler RP. | Respir Res. 2014 Oct 12;15:127. doi: 10.1186/s12931-014-0127-9. | Respir Res. 2014 | PubMed | citation | PMID:25306249 | PMCID:PMC4198701 | pubmed | 25306249 | create date:2014/10/13 | first author:Carolan BJ |
| 8 | 1 |  | 1 | Smoking | Soluble receptor for advanced glycation end-products and progression of airway disease. | BACKGROUND: The receptor for advanced glycation end-products (RAGE) is highly expressed in the lung, where it is believed to have a homeostatic role. Reduced plasma levels of soluble RAGE (sRAGE) have been reported in patients with chronic obstructive pulmonary disease (COPD). The aim of the present study was to evaluate the association of plasma sRAGE levels with a longitudinal decline of lung function. We have also measured plasma levels of high mobility group box 1 (HMGB1), a RAGE ligand which has been associated with chronic inflammatory diseases including COPD.  METHODS: Baseline plasma concentrations of sRAGE and HMGB1 were measured in non-smokers (n = 32), smokers without COPD (n = 212), and smokers with COPD (n = 51), and the associations of the plasma sRAGE and HMGB1 levels with longitudinal declines of lung function during a 4-year follow-up period were analysed.  RESULTS: The plasma levels of sRAGE were significantly lower in smokers without COPD and in smokers with COPD, as compared to those of non-smokers. Plasma sRAGE levels positively correlated with FVC and FEV1 and inversely correlated with BMI and pack-years. Lower sRAGE levels were associated with greater declines of FEV1/FVC over 4 years in all participants. Moreover, multivariate regression analysis indicated that the baseline plasma sRAGE concentration was an independent predictor of FEV1/FVC decline in all groups. A subgroup analysis showed that decreased sRAGE levels are significantly associated with a more rapid decline of FEV1/FVC in smokers with COPD. There was no significant correlation between plasma HMGB1 levels and longitudinal decline of lung function.  CONCLUSIONS: Lower plasma concentrations of sRAGE were associated with greater progression of airflow limitations over time, especially in smokers with COPD, suggesting that RAGE might have a protective role in the lung. | /pubmed/24758342 | Iwamoto H, Gao J, Pulkkinen V, Toljamo T, Nieminen P, Mazur W. | BMC Pulm Med. 2014 Apr 24;14:68. doi: 10.1186/1471-2466-14-68. | BMC Pulm Med. 2014 | PubMed | citation | PMID:24758342 | PMCID:PMC4021457 | pubmed | 24758342 | create date:2014/04/25 | first author:Iwamoto H |
| 9 | 1 |  | 1 | Smoking | Overexpression of RAGE contributes to cigarette smoke-induced nitric oxide generation in COPD. | BACKGROUND: Receptor for advanced glycation end products (RAGE), a multiple-ligands receptor, is implicated in chronic obstructive pulmonary disease (COPD). This study was designed to investigate the potential role of RAGE in nitric oxide (NO) generation, an endogenous marker of nitrosative stress in COPD.  METHODS: Lung tissues from COPD patients were used to describe the relationship between RAGE expression and NO level. RAGE 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 was used to detect the role of RAGE in CSE-induced NO generation by 16HBE cells.  RESULTS: Compared with nonsmoker controls, overexpression of RAGE was significantly detected in COPD smokers (p < 0.01), but not healthy smokers and nonsmokers with COPD, which was dominantly expressed at bronchiolar epithelia. Correlation analysis showed that RAGE in COPD smokers was positively related to NO level, smoking status, and lung function decline. In cultured 16HBE cells treated with CSE, soluble RAGE was reduced; however, full-length RAGE was enhanced significantly as the same trend as NO generation. Moreover, increased NO level and NO synthase activity, decreased total glutathione (a major cellular antioxidant), enhanced nuclear translocation of p65 (a key molecule of nuclear factor (NF)-κB) and release of NF-κB-dependent proinflammatory cytokines were all reversed by pretreatment of anti-RAGE antibody.  CONCLUSIONS: These findings suggest that overexpression of RAGE contributes to CS-induced NO generation in COPD with involvement in NF-κB activation. | /pubmed/24535058 | Chen L, Wang T, Guo L, Shen Y, Yang T, Wan C, Liao Z, Xu D, Wen F. | Lung. 2014 Apr;192(2):267-75. doi: 10.1007/s00408-014-9561-1. Epub 2014 Feb 18. | Lung. 2014 | PubMed | citation | PMID:24535058 | pubmed | 24535058 | create date:2014/02/19 | first author:Chen L |
| 10 | 1 | smoking assoc COPD compared with healthy controls | 1 | Smoking | Association of polymorphisms of the receptor for advanced glycation end products gene with COPD in the Chinese population. | The receptor for advanced glycation end products (RAGE) is a cell surface molecule of the immunoglobulin superfamily that binds diverse endogenous ligands involved in the development of chronic diseases and inflammatory damage. A growing body of evidence has suggested that RAGE is involved in the development and progression of chronic obstructive pulmonary disease (COPD). The present study investigated the existence of an association among three polymorphisms (-374T/A, -429T/C, and G82S) of the RAGE gene with the risk of COPD in the Chinese population. The RAGE genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism in 216 patients with COPD and 239 age-matched healthy individuals. Our study demonstrated that the frequencies of the GS genotype and the S allele in the G82S mutation were significantly higher in COPD patients than in controls (odds ratios [OR]=1.70, 95% confidence interval [CI]: 1.15-2.50, p=0.0098 and OR=1.42, 95% CI: 1.06-1.91, p=0.023, respectively). Further stratification analysis by smoking status revealed that the presence of the GS genotype conferred a higher risk of developing COPD in current smokers (p=0.044). In contrast, mutations at -374T/A and -429T/C did not demonstrate any association with COPD, even after taking into account the patients' smoking history. Our study provides preliminary evidence that the G82S polymorphism in the RAGE gene is associated with an increased risk of COPD and that the GS genotype of the G82S variant is a risk factor for COPD in the Chinese population. | /pubmed/24520905 | Li Y, Yang C, Ma G, Gu X, Chen M, Chen Y, Zhao B, Cui L, Li K. | DNA Cell Biol. 2014 Apr;33(4):251-8. doi: 10.1089/dna.2013.2303. Epub 2014 Feb 12. | DNA Cell Biol. 2014 | PubMed | citation | PMID:24520905 | PMCID:PMC3967375 | pubmed | 24520905 | create date:2014/02/14 | first author:Li Y |
| 11 | 1 | smoking assoc COPD compared with healthy controls (eclipse) | 1 | Smoking | The presence and progression of emphysema in COPD as determined by CT scanning and biomarker expression: a prospective analysis from the ECLIPSE study. | BACKGROUND: 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 explored the potential relation between emphysema and patient characteristics, and investigated if certain circulating biomarkers were associated with decline in CT lung density.  METHODS: We used a random coefficient model to assess predictors of both CT lung density and its longitudinal change over 3 years in 1928 patients with COPD enrolled in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study. Lung density was measured for every voxel in the CT scan and after correcting for lung volume was expressed as the density at lowest 15th percentile point of the distribution. This study is registered with ClinicalTrials.gov, number NCT00292552.  FINDINGS: Lung density at baseline was influenced by age, sex, body-mass index, current smoking status and smoking history, and severity of airflow limitation. The observed decline in lung density was variable (mean decline -1·13 g/L [SE 0·06] per year). The annual decline in lung density was more rapid in women (additional -0·41 [SE 0·14] g/L per year, p=0·003) than men and in current smokers (additional -0·29 [SE 0·14] g/L per year, p=0·047) than in former smokers. Circulating levels of the biomarkers surfactant protein D (SP-D) and soluble receptor for advanced glycation endproduct (sRAGE) were significantly associated with both baseline lung density and its decline over time.  INTERPRETATION: This study shows that decline in lung density in COPD can be measured, that it is variable, and related to smoking and gender. We identified potential biochemical predictors of the presence and progression of emphysema. | /pubmed/24429093 | Coxson HO, Dirksen A, Edwards LD, Yates JC, Agusti A, Bakke P, Calverley PM, Celli B, Crim C, Duvoix A, Fauerbach PN, Lomas DA, Macnee W, Mayer RJ, Miller BE, MÃ¼ller NL, Rennard SI, Silverman EK, Tal-Singer R, Wouters EF, Vestbo J; Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators.. | Lancet Respir Med. 2013 Apr;1(2):129-36. doi: 10.1016/S2213-2600(13)70006-7. Epub 2013 Feb 1. | Lancet Respir Med. 2013 | PubMed | citation | PMID:24429093 | pubmed | 24429093 | create date:2014/01/17 | first author:Coxson HO |
| 12 | 1 | copd and smoking | 1 | Smoking | Systemic biomarkers of neutrophilic inflammation, tissue injury and repair in COPD patients with differing levels of disease severity. | The identification and validation of biomarkers to support the assessment of novel therapeutics for COPD continues to be an important area of research. The aim of the current study was to identify systemic protein biomarkers correlated with measures of COPD severity, as well as specific protein signatures associated with comorbidities such as metabolic syndrome. 142 protein analytes were measured in serum of 140 patients with stable COPD, 15 smokers without COPD and 30 non-smoking controls. Seven analytes (sRAGE, EN-RAGE, NGAL, Fibrinogen, MPO, TGF-α and HB-EGF) showed significant differences between severe/very severe COPD, mild/moderate COPD, smoking and non-smoking control groups. Within the COPD subjects, univariate and multivariate analyses identified analytes significantly associated with FEV(1), FEV(1)/FVC and DLCO. Most notably, a set of 5 analytes (HB-EGF, Fibrinogen, MCP-4, sRAGE and Sortilin) predicted 21% of the variability in DLCO values. To determine common functions/pathways, analytes were clustered in a correlation network by similarity of expression profile. While analytes related to neutrophil function (EN-RAGE, NGAL, MPO) grouped together to form a cluster associated with FEV(1) related parameters, analytes related to the EGFR pathway (HB-EGF, TGF-α) formed another cluster associated with both DLCO and FEV(1) related parameters. Associations of Fibrinogen with DLCO and MPO with FEV(1)/FVC were stronger in patients without metabolic syndrome (r  =  -0.52, p  =  0.005 and r  =  -0.61, p =  0.023, respectively) compared to patients with coexisting metabolic syndrome (r  =  -0.25, p  =  0.47 and r  =  -0.15, p  =  0.96, respectively), and may be driving overall associations in the general cohort. In summary, our study has identified known and novel serum protein biomarkers and has demonstrated specific associations with COPD disease severity, FEV(1), FEV(1)/FVC and DLCO. These data highlight systemic inflammatory pathways, neutrophil activation and epithelial tissue injury/repair processes as key pathways associated with COPD. | /pubmed/22701684 | Cockayne DA, Cheng DT, Waschki B, Sridhar S, Ravindran P, Hilton H, Kourteva G, Bitter H, Pillai SG, Visvanathan S, MÃ¼ller KC, Holz O, Magnussen H, Watz H, Fine JS. | PLoS One. 2012;7(6):e38629. doi: 10.1371/journal.pone.0038629. Epub 2012 Jun 12. | PLoS One. 2012 | PubMed | citation | PMID:22701684 | PMCID:PMC3373533 | pubmed | 22701684 | create date:2012/06/16 | first author:Cockayne DA |
| 13 | 1 | copd, not environmental exposure | 1 | Smoking | CHRNA3/5, IREB2, and ADCY2 are associated with severe chronic obstructive pulmonary disease in Poland. | We examined the association between single-nucleotide polymorphisms (SNPs) previously associated with chronic obstructive pulmonary disease (COPD) and/or lung function with COPD and COPD-related phenotypes in a novel cohort of patients with severe to very severe COPD. We examined 315 cases of COPD and 330 Caucasian control smokers from Poland. We included three SNPs previously associated with COPD: rs7671167 (FAM13A), rs13180 (IREB2), and rs8034191 (CHRNA 3/5), and four SNPs associated with lung function in a genome-wide association study of general population samples: rs2070600 (AGER), rs11134242 (ADCY2), rs4316710 (THSD4), and rs17096090 (INTS12). We tested for associations with severe COPD and COPD-related phenotypes, including lung function, smoking behavior, and body mass index. Subjects with COPD were older (average age 62 versus 58 years, P < 0.01), with more pack-years of smoking (45 versus 33 pack-years, P < 0.01). CHRNA3/5 (odds ratio [OR], 1.89; 95% confidence interval [CI], 1.5-2.4; P = 7.4 × 10(-7)), IREB2 (OR, 0.69; 95% CI, 0.5-0.9; P = 3.4 × 10(-3)), and ADCY2 (OR, 1.35; 95% CI, 1.1-1.7; P = 0.01) demonstrated significant associations with COPD. FAM13A (OR, 0.8; 95% CI, 0.7-1.0; P = 0.11) approached statistical significance. FAM13A and ADCY2 also demonstrated a significant association with lung function. Thus, in severe to very severe COPD, we demonstrate a replication of association between two SNPs previously associated with COPD (CHRNA3/5 and IREB2), as well as an association with COPD of one locus initially associated with lung function (ADCY2). | /pubmed/22461431 | Hardin M, Zielinski J, Wan ES, Hersh CP, Castaldi PJ, Schwinder E, Hawrylkiewicz I, Sliwinski P, Cho MH, Silverman EK. | Am J Respir Cell Mol Biol. 2012 Aug;47(2):203-8. doi: 10.1165/rcmb.2012-0011OC. Epub 2012 Mar 29. | Am J Respir Cell Mol Biol. 2012 | PubMed | citation | PMID:22461431 | PMCID:PMC3423462 | pubmed | 22461431 | create date:2012/03/31 | first author:Hardin M |
| 14 | 1 | copd, not environmental exposure | 1 | Smoking | Soluble receptor for advanced glycation end products in COPD: relationship with emphysema and chronic cor pulmonale: a case-control study. | BACKGROUND: The receptor for advanced glycation end products (RAGE) is a multiligand signal transduction receptor that can initiate and perpetuate inflammation. Its soluble isoform (sRAGE) acts as a decoy receptor for RAGE ligands, and is thought to afford protection against inflammation. With the present study, we aimed at determining whether circulating sRAGE is correlated with emphysema and chronic cor pulmonale in chronic obstructive pulmonary disease (COPD).  METHODS: In 200 COPD patients and 201 age- and sex-matched controls, we measured lung function by spirometry, and sRAGE by ELISA method. We also measured the plasma levels of two RAGE ligands, N-epsilon-carboxymethyl lysine and S100A12, by ELISA method. In the COPD patients, we assessed the prevalence and severity of emphysema by computed tomography (CT), and the prevalence of chronic cor pulmonale by echocardiography. Multiple quantile regression was used to assess the effects of emphysema, chronic cor pulmonale, smoking history, and comorbid conditions on the three quartiles of sRAGE.  RESULTS: sRAGE was significantly lower (p = 0.007) in COPD patients (median 652 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 the severity of emphysema (p < 0.001), the lower the level of sRAGE the greater the degree of emphysema on CT. The relationship 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 (p = 0.002). Such difference remained statistically significant after adjusting for smoking history, comorbidities, and emphysema severity. There was no significant difference in the plasma levels of the two RAGE ligands between cases and controls.  CONCLUSIONS: sRAGE is significantly lower in patients with COPD than in age- and sex-matched individuals without airflow obstruction. Emphysema and chronic cor pulmonale are independent predictors of reduced sRAGE in COPD. | /pubmed/21450080 | Miniati M, Monti S, Basta G, Cocci F, Fornai E, Bottai M. | Respir Res. 2011 Mar 30;12:37. doi: 10.1186/1465-9921-12-37. | Respir Res. 2011 | PubMed | citation | PMID:21450080 | PMCID:PMC3072955 | pubmed | 21450080 | create date:2011/04/01 | first author:Miniati M |
| 15 | 1 | not discussing environmental exposure assoc OAD | 1 | Smoking | Proteomic studies on receptor for advanced glycation end product variants in idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. | PURPOSE: Proteomic screening revealed declined levels of the 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 obstructive pulmonary disease (COPD).  EXPERIMENTAL DESIGN: RAGE was analyzed by 2-DE, MS and Western blotting using lung tissues from non-smokers, smokers, patients with IPF, COPD and α-1-antitrypsin deficiency (AAT) and by ELISA from the bronchoalveolar lavage fluid samples.  RESULTS: RAGE, detected by 2-DE in the control lung, was confirmed to be glycosylated, soluble, C-truncated RAGE with characteristics indicative of the presence of endogenous secretory RAGE (esRAGE). Further studies revealed a decrease of the full length-RAGE (FL-RAGE) and its C-terminal processed variant (cRAGE) in the lung tissues of IPF and COPD patients but not in AAT. The esRAGE level was reduced in IPF but was unchanged in COPD.  CONCLUSIONS AND CLINICAL RELEVANCE: This study shows an involvement of the three RAGE variants (FL-RAGE, cRAGE, esRAGE) in IPF. The decline of FL-RAGE and cRAGE, but not esRAGE, in COPD lungs is evidence of involvement of specific RAGE variants also in this disease. | /pubmed/21137019 | Ohlmeier S, Mazur W, Salmenkivi K, MyllÃ¤rniemi M, Bergmann U, Kinnula VL. | Proteomics Clin Appl. 2010 Jan;4(1):97-105. doi: 10.1002/prca.200900128. Epub 2010 Jan 7. | Proteomics Clin Appl. 2010 | PubMed | citation | PMID:21137019 | pubmed | 21137019 | create date:2010/12/08 | first author:Ohlmeier S |
| 16 | 1 | copd, not environmental exposure | 1 | Smoking | Expression of high-mobility group box 1 and of receptor for advanced glycation end products in chronic obstructive pulmonary disease. | RATIONALE: Chronic obstructive pulmonary disease (COPD) is characterized by airway inflammation and remodeling. High-mobility group box 1 (HMGB1), a nuclear protein that is released during inflammation and repair, interacts with proinflammatory cytokines and with the receptor for advanced glycation end products (RAGE), which is highly expressed in the lung.  OBJECTIVES: To determine whether HMGB1 is augmented in COPD and is associated with IL-1beta 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-1beta in human macrophages and in BAL fluid was examined.  MEASUREMENTS AND MAIN 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-1beta (r(s) = 0.438; P = 0.0006) and negatively with FEV(1) (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-1beta 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-alpha. 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-1beta and RAGE. | /pubmed/20133931 | Ferhani N, Letuve S, Kozhich A, Thibaudeau O, Grandsaigne M, Maret M, Dombret MC, Sims GP, Kolbeck R, Coyle AJ, Aubier M, Pretolani M. | Am J Respir Crit Care Med. 2010 May 1;181(9):917-27. doi: 10.1164/rccm.200903-0340OC. Epub 2010 Feb 4. | Am J Respir Crit Care Med. 2010 | PubMed | citation | PMID:20133931 | pubmed | 20133931 | create date:2010/02/06 | first author:Ferhani N |
| 17 | 1 |  | 1 | Smoking | A genome-wide association study of emphysema and airway quantitative imaging phenotypes. | Rationale: 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 or spirometry. In addition, we sought to determine whether previously described genome-wide significant COPD and spirometric loci were associated with emphysema or airway phenotypes. Objectives: To identify genetic determinants of quantitative imaging phenotypes. Methods: We performed a GWAS on two quantitative emphysema and two quantitative airway imaging phenotypes in the COPDGene (non-Hispanic white and African American), ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints), NETT (National Emphysema Treatment Trial), and GenKOLS (Genetics of COPD, Norway) studies and on percentage gas trapping in COPDGene. 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 risk factors for quantitative imaging characteristics in COPD and also identify imaging features associated with previously identified lung function loci | [Click here for full text options](http://ezproxy.library.nyu.edu:2048/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed17&AN=606146088) | Cho M.H.  Castaldi P.J.  Hersh C.P.  Hobbs B.D.  Barr R.G.  Tal-Singer R.  Bakke P.  Gulsvik A.  San Jose Estepar R.  Van Beek E.J.R.  Coxson H.O.  Lynch D.A.  Washko G.R.  Laird N.M.  Crapo J.D.  Beaty T.H.  Silverman E.K. | American Journal of Respiratory and Critical Care Medicine. 192 (5) (pp 559-569), 2015. Date of Publication: 01 Sep 2015. | American Thoracic Society (E-mail: malexander@thoracic.org) | Embase | Article |  |  |  |  |
| 18 | 1 | copd, not environmental | 1 | Smoking | Changes of HMGB1 and sRAGE during the recovery of COPD exacerbation. | Background: Acute exacerbation of chronic obstructive pulmonary disease is associated with increased airway and systemic inflammation. However, the correlation between acute exacerbation/convalescence of chronic obstructive pulmonary disease (COPD) and simultaneous changes of 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. **Methods:** A total of 44 COPD patients were recruited. Following a structured interview, plasma levels of HMGB1, sRAGE, fibrinogen and serum level of high-sensitivity C-reactive protein (hsCRP) were measured in patients with acute exacerbation of COPD (AECOPD) within 24 h of hospitalization and pre-discharge (convalescence). All patients were examined with spirometry in convalescence of COPD. Results: There was a significant decline in plasma HMGB1 (P<0.01), sRAGE (P<0.05), fibrinogen (P<0.01) and serum hsCRP (P<0.01) levels from acute exacerbation to convalescence phase of COPD. Changes of sRAGE was significantly correlated with changes of HMGB1 (r=0.4, P=0.007). COPD disease status correlated 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 higher than ex-smoker group in either phase of COPD. Conclusions: HMGB1 and sRAGE levels 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 | [Click here for full text options](http://ezproxy.library.nyu.edu:2048/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed16&AN=373623472) | Zhang Y.  Li S.  Wang G.  Han D.  Xie X.  Wu Y.  Xu J.  Lu J.  Li F.  Li M. | Journal of Thoracic Disease. 6 (6) (pp 734-741), 2014. Date of Publication: 2014. | Pioneer Bioscience Publishing (E-mail: jtd@thepbpc.org) | Embase | Article |  |  |  |  |
| 19 | 1 |  | 1 | Smoking | Plasma sRAGE and N-(carboxymethyl) lysine in patients with CHF and/or COPD. | Background: Knowledge of the role of the receptor for advanced glycation end products (RAGE), particularly its soluble form (sRAGE), and of its advanced glycation end product (AGE) ligand, N-(carboxymethyl)lysine adducts (CML), is limited in chronic heart failure (CHF) and in chronic obstructive pulmonary disease (COPD). We evaluated whether the AGE/RAGE system is activated in stable CHF and COPD, and whether plasma sRAGE and CML levels are affected by clinical and functional parameters. **Materials and methods:** We measured plasma levels of sRAGE and CML using a sandwich enzyme-linked immunosorbent assay (ELISA) in 143 subjects, aged >= 65 years, divided into five groups: 58 with CHF, 23 with COPD, 27 with CHF+COPD and 35 controls (17 healthy smokers and 18 healthy nonsmokers). Individuals with diabetes were excluded from the study. Results: Plasma levels of sRAGE and CML were higher in CHF patients than in controls [sRAGE: 0.48 (0.37-0.83) vs. 0.42 (0.29-0.52) ng/mL, P = 0.01; CML: 1.95 (1.58-2.38) vs. 1.68 (1.43-2.00) ng/mL, P = 0.01]. By contrast, sRAGE and CML were not different between both COPD and CHF+COPD patients and controls (P > 0.05). N-terminal pro-brain natriuretic peptide (Nt-pro BNP) correlated with sRAGE, but not with CML, in the patient groups: CHF (r = 0.43, P < 0.001), COPD (r = 0.77, P < 0.0001) and CHF/COPD (r = 0.43, P = 0.003). Conclusions: Plasma levels of sRAGE and CML are increased in CHF, but not in COPD patients. The robust association between NT-pro BNP, a diagnostic and prognostic marker in CHF, and sRAGE concentrations might suggest a possible BNP pathway of amplification of inflammation via the AGE/RAGE system | [Click here for full text options](http://ezproxy.library.nyu.edu:2048/login?url=http://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=emed15&AN=52553278) | Boschetto P.  Campo I.  Stendardo M.  Casimirri E.  Tinelli C.  Gorrini M.  Ceconi C.  Fucili A.  Potena A.  Papi A.  Ballerin L.  Fabbri L.  Luisetti M. | European Journal of Clinical Investigation. 43 (6) (pp 562-569), 2013. Date of Publication: June 2013. | Blackwell Publishing Ltd (9600 Garsington Road, Oxford OX4 2XG, United Kingdom) | Embase | Article |  |  |  |  |