S119 MICRORNA-200B REPRESSES TGF- β1 INDUCED EMT IN BEAS-2B AND PRIMARY BRONCHIAL EPITHELIAL CELLS

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Introduction MicroRNAs (miRNAs) are small non-coding RNAs that function as endogenous gene regulators. They may initiate a process called epithelial-mesenchymal transition (EMT) that leads to aberrant extracellular matrix remodelling and is implicated in a number of airway diseases. Dysregulation of miRNAs has been indicated in chronic lung disorders, the third most common cause of mortality in adults.

Materials and methods NanoString was used to assay the differential expression of miRNAs at 1, 4 and 24 hrs following TGF-β1 treatment of BEAS-2B cells (immortalised primary bronchial epithelial cells) and control. QRT-PCR validated the expression profile of miR-200b. BEAS-2B and PBECs (primary bronchial epithelial cells) were transfected with miR-200b mimics to study expression of EMT markers at mRNA and protein level. MiRNA targets were identified and validated using multiple computational tools and qRT-PCR respectively.

Results nCounter assay allowed identification of novel miRNAs including miR-200 family. MiR-200b mimic transfection (24 hrs) followed by TGF-β1 treatment (48 hrs) demonstrated a significant increase in E-Cadherin ($p \leq 0.05$, $p \leq 0.001$) and a significant decrease in Fibronectin ($p \leq 0.001$, $p \leq 0.01$) in BEAS-2B cells and PBECs. Protein studies suggested a similar trend in both the cells. The most prominent targets of miR-200b identified were RHOA, SMURF2, ZNF532 and ZEB2. A significant decrease was observed in ZNF532 ($p \leq 0.01$) and ZEB2 ($p \leq 0.001$) in miR-200b transfected and TGF-β1 treated BEAS-2B cells ($n = 3$). Differential expression of mRNA targets was observed in two sets of patient derived PBECs.

Conclusion miR-200b suppressed TGF-β1 induced EMT by maintaining the epithelial framework of BEAS-2B cells and PBECs. Results provide new insights into miR-200b regulation in fibrosis and basis for therapeutic application in lung injury.

S120 SERUM MICRORNA PROFILES IN IPF PATIENTS – BIOMARKERS OR POTENTIAL THERAPEUTIC TARGETS?

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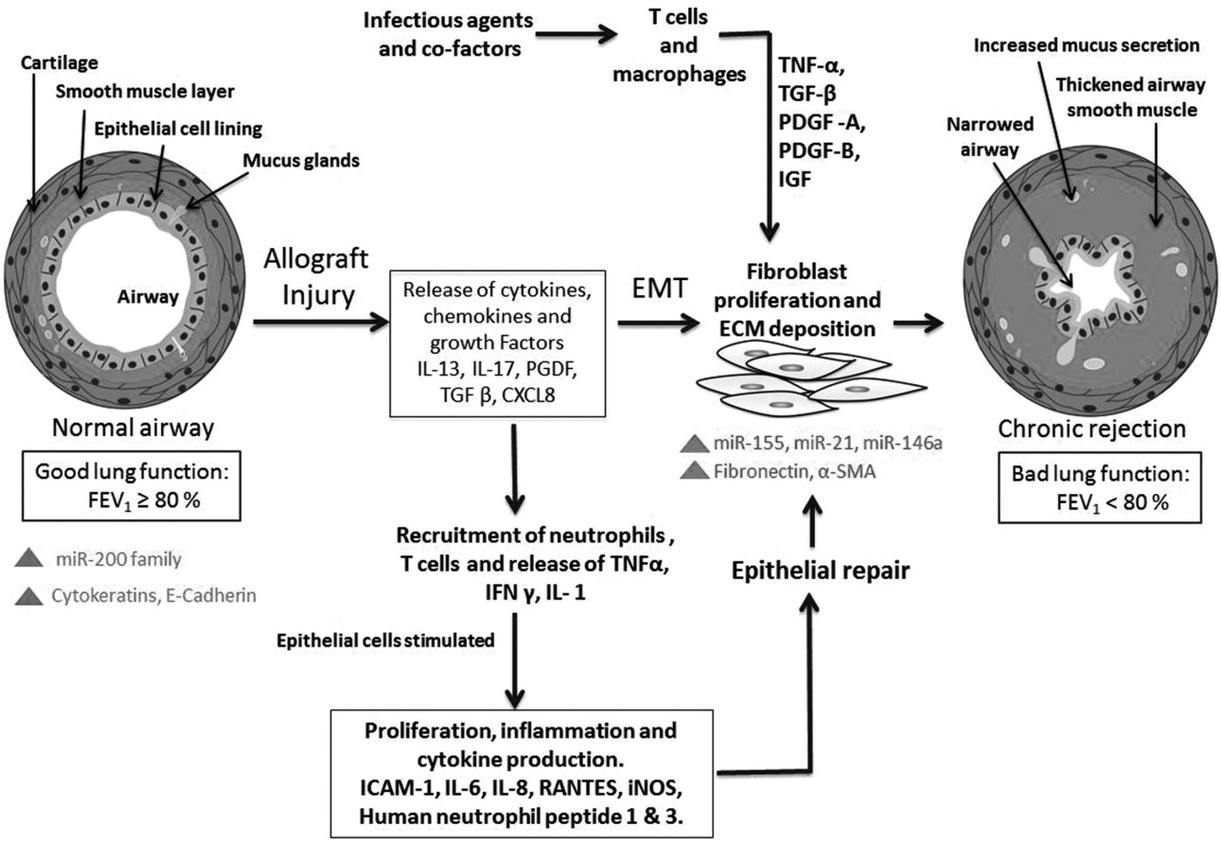
Introduction and objectives Idiopathic Pulmonary Fibrosis (IPF) has limited therapeutic options and predicting the natural history in individual cases is difficult. Exosomes are extracellular microvesicles that are involved in cell-cell signalling. MicroRNA isolated from exosomes has been implicated in several fibrotic models.[1] At present the role of miRNAs in development of lung fibrosis is unclear. We aim to characterise miRNAs isolated from IPF patients and relate these to measures of disease severity.

Methods We assessed exosomes isolated from the serum of IPF patients ($n = 8$) and aged matched healthy controls ($n = 6$). Exosomes were characterised by western blot and Nanosight



Abstract S119 Figure 1

technology. MiRNA was isolated from these exosomes and profiled using a miRNA PCR assay. Demographic and clinical data was extracted from clinical records. IPF patients were stratified by radiological severity, GAP scoring and rate of progression.

Results Exosomes isolated from IPF patients demonstrated decreased fold regulation in antifibrotic miRNA such as miR-141 and miR-29 in addition to increases in fibrogenic miRNA such as miR-7 when compared to healthy controls. The degree of up regulation in miR-7 correlates significantly with stratified burden of disease. Interestingly down regulation of miR-155 was also found which has been previously associated with up regulation in mice fibrosis models. Patients had a median follow up of 31 months (IQR 17–43). There was a significant correlation with regards to up regulation of miR-125b with milder disease defined by the GAP score and preservation of FVC.

Conclusion This data identifies novel biomarkers that may provide insights into the natural history and pathogenesis of the disease. Furthermore miR-7 and miR-29 have been implicated in extracellular matrix remodelling with target genes including ECM proteins such as collagens, fibrillins and elastin. Inhibiting up regulated miRNA or supplementing down regulated miRNA may be potential therapeutic targets.

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COPD weighs heavy on the heart

S121 CO-MORBIDITY AND PNEUMONIA RISK IN COPD PATIENTS: A POPULATION DATABASE ANALYSIS OF PRIMARY CARE PATIENTS

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Background Co-morbidities are common in COPD and have been associated with poorer clinical outcomes. Furthermore, patients with COPD are at an increased risk of developing Community acquired pneumonia (CAP). We investigated the impact of concurrent co-morbidity on the risk of developing CAP, in a cohort of COPD patients identified from the Hampshire Health Record analytical database, a local NHS database containing anonymised primary and secondary care records.

Methods Patients defined as having COPD, had a diagnostic Read code (classification of clinical terms for electronic information coding) in their primary care record at any time prior to 1st January 2010 and were aged ≥40 years at the start of the study period. Using clinician-coded diagnoses, CAP episodes which occurred over a 1-year period from the 1st January 2010 were identified using Read and ICD-10 code lists and were defined as taking up to 70 days to resolve. Listed co-morbidities were based on coded entries at any time prior to 1st January 2010.

Results Included were 6707 patients with a complete history in 2010 and valid data for all variables considered in the analysis. 55% of patients were men and 36% were current smokers, the mean age was 70 years. 189 patients (2.8%) had at least one CAP episode during 2010. Compared to patients without CAP, patients with CAP were more likely to have ischaemic heart disease (IHD p = 0.005), congestive heart failure (CHF p = 0.021), hypertension (p = 0.017), cerebrovascular disease (CVD p < 0.001), dementia (p < 0.001), and bronchiectasis (p = 0.001). Using logistic regression and controlling for potential confounders, CVD and dementia were independent risk factors for CAP (p = 0.009 and 0.007, respectively), while bronchiectasis trended towards significance (p = 0.073) (Table 1).

Abstract S121 Table 1 Co-morbidities associated with CAP occurrence in COPD

Co-morbidity	Odds ratio	95 % confidence interval	P-value
IHD	1.13	0.80 – 1.59	0.478
CHF	1.11	0.65 – 1.89	0.712
Hypertension	1.18	0.87 – 1.60	0.276
CVD	1.73	1.15 – 2.62	**0.009**
Dementia	2.95	1.35 – 6.48	**0.007**
Bronchiectasis	1.70	0.95 – 3.04	0.073

Odds ratios, 95% confidence intervals and p-values were calculated from logistic regression. Separate regression models were used for each co-morbidity, controlling for number of exacerbations in 2010, age, sex, smoking status, inhaled corticosteroid use and MRC dyspnoea score.

Conclusion In this large population database analysis, CVD and dementia were identified as being independently associated with an increased risk of CAP. Oro-pharyngeal dysfunction in CVD and use of sedative medications in dementia, may contribute to these findings. Further analysis of the complete cohort, over the full 5-year observation period will allow the formulation of robust conclusions about the important factors of CAP risk in COPD, including the impact of pharmacotherapy, blood markers and functional parameters.

S122 THE EFFECT OF BODY MASS INDEX ON PATIENT OUTCOME IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A RETROSPECTIVE COHORT STUDY USING THE HAMPSHIRE HEALTH RECORD

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Introduction and objectives Chronic obstructive pulmonary disease (COPD) is a systemic disease characterised by persistent airflow obstruction but also has significant extra-pulmonary manifestations, including effects on body mass index (BMI). Nutritional status has been implicated as a predictor of outcome. We aimed to investigate the relationship between BMI and outcomes in a representative sample of UK COPD patients.

Method Patients with a coded GP diagnosis of COPD on or before 31/12/2010 and full data for 3 years or until death were identified from the Hampshire Health Record Analytical database, which collects anonymised routine clinical care data from GP and hospital computer records. Subjects were categorised as underweight, normal, overweight, obese or very obese by WHO standards. Outcomes measured were all-cause death and respiratory-cause hospitalisation and emergency department attendance rate in the following 3 years. Multivariate cox regression modelling was used to estimate hazard ratio (HR) and confidence intervals (CI) adjusted for age, gender, smoking status and FEV_1%predicted.