

pulmonary arterial hypertension (PAH), a condition associated with pulmonary vascular cell proliferation. Methylation on histone H3K27 (H3K27me3) has been found to be a key regulator of development and cell homeostasis. Methylation at H3K27 can be reversed by the Jumonji C (JmjC) domain-containing proteins, JMJD3 and UTX.

Methods Immunohistochemistry for JMJD3, UTX and H3K27me3 was performed on lungs from a monocrotaline (MCT) rat model of PAH, in control animals and in patients with idiopathic PAH and healthy control subjects.

Results In the rat MCT model of PAH, we found that the expression of JMJD3 protein is increased in all three cell layers (endothelial cells, smooth muscle cells and fibroblasts) in remodelled pulmonary arterioles (PA). The greatest increase is within endothelial cells, particularly in partially occluded or completely occluded PA (Appendix Figure 1). In contrast, the expression of UTX is unchanged. There was a corresponding decrease in H3K27me3 staining in remodelled PA and some cells completely lost H3K27me3 expression. JMJD3 protein expression was also found in remodelled PA in the lung of patients with iPAH especially in endothelial cells and the plexiform lesion.

Conclusion Our data suggest that JMJD3 expression and H3K27 histone methylation could play an important role in the pathogenesis of iPAH. The rat MCT model of PAH is a suitable model for further mechanistic and intervention studies.

Phenotyping and treating severe asthma

S7 AIRWAY PATHOLOGICAL PHENOTYPES AND THEIR CLINICAL UTILITY IN ADULT ASTHMA

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Background Airway remodelling and cellular inflammation are well recognised pathological features of asthma. However the relationship between asthma phenotype, treatment intensity and pathology is poorly understood.

Objectives We performed a study of common pathological features in adult asthmatic bronchial biopsies to identify (i) whether discrete 'pathological phenotypes/subtypes' exist and (ii) their clinical utility.

Methods 202 patients (142 asthma and 60 healthy volunteers) were recruited. Patients underwent bronchoscopy and endobronchial biopsy. Bronchial biopsies were evaluated for eleven common features of asthma pathology. Standard biostatistical analyses including a range of cluster analyses and machine learning were applied to pathological features alone to evaluate our objectives.

Results Three distinct immunopathological clusters were identified and characterised by distinct biopsy features of cellular inflammation and remodelling. Specifically, i) late onset severe eosinophilic asthma [cluster 1] with evidence of reticular basement membrane thickening, increased epithelial area and vascular remodelling, ii) milder late onset asthma [cluster 2] with few features of remodelling and iii), an early onset atopic eosinophilic asthma [cluster 3] with features of Th2 high asthma, increased airway smooth muscle (ASM) mass, increased

mast cells within the ASM and a mixed granulocytic submucosal inflammation. Pre bronchodilator FEV1 and decline (in a subset) differed across the clusters. Pathological features did not add value to the clinical prediction of asthma.

Conclusion We have identified three novel pathological clusters of asthma with differing features of airway remodelling, cellular inflammation and airway function. Asthma may be characterised by variable pathological phenotypes warranting further evaluation in larger population studies.

S8 A NATIONWIDE REAL-LIFE STUDY: EXPLORING THE DIFFICULTIES OF CONFIRMING THE ASTHMA DIAGNOSIS IN PATIENTS WITH SEVERE ASTHMA

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Introduction Many conditions may mimic severe asthma. Therefore, patients with asthma who receive high dose asthma therapy are recommended to undergo systematic evaluation in order to objectively confirm the diagnosis of asthma.

Aims and objectives To evaluate to which extent patients treated by respiratory specialists for severe asthma had the diagnosis of asthma verified by the demonstration of variable airflow obstruction.

Methods A retrospective cross-sectional study was performed in 2013. Patient record forms of all patients (18–65 years) newly referred to one of five respiratory outpatient clinics in Denmark in the period of 2009–2010 with a diagnose of asthma (ICD-10: DJ45-DJ459) were screened after a two-year observation period for having severe asthma. Patients were included in the study, if they had a doctors diagnosis of asthma and received inhaled corticosteroids equivalent to ≥ 1600 μ g budesonide and a second controller (long acting beta-2-agonist, theophylline or leukotriene-antagonist) for a minimum of twelve months or were treated with oral prednisolone (minimum six months). Diagnostic tests for asthma were registered: Day-to-day PEF monitoring, reversibility test (short-acting beta-2-agonist or prednisolone) and bronchial challenge test (methacholine, mannitol, exercise test, eucapnic voluntary hyperpnoea test).

Results A total of 1417 newly referred subjects were screened, of whom 98 patients fulfilled the above criteria of having severe asthma. Overall, 84% were assessed with at least one diagnostic test: Reversibility test 63%, PEF monitoring 57% and bronchial challenge test 21%.

In total, 50% of the study population had at least one positive diagnostic test; 37% had a positive reversibility test, 17% had significant peak flow variation and 12% had a positive bronchial challenge test. Among those having negative reversibility test or negative peak flow measurements with FEV1 $\geq 70\%$, only 30% had a bronchial challenge test performed.

Conclusion Among patients managed for severe asthma in five specialist hospital clinics in Denmark, only half had the asthma diagnosis confirmed objectively. This indicates a substantial room for improvement in order to ensure that patients receiving high dose asthma therapy truly have asthma.