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PATHOPHYSIOLOGY OF ASTHMA: EOSINOPHILIA AND NEUTROPHILIA

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Annotation: *Asthma is a condition in which your airways narrow and swell and may produce extra mucus. This can make breathing difficult and trigger coughing, a whistling sound (wheezing) when you breathe out and shortness of breath. For some people, asthma is a minor nuisance. For others, it can be a major problem that interferes with daily activities and may lead to a life-threatening asthma attack.*

Key words: *biomarker, transcriptomics, bronchial biopsy, bronchial brushings, induced sputum, airway inflammation, asthma phenotype, endotype.*

INTRODUCTION

Asthma describes a clinical syndrome of wheeze, breathlessness, chest tightness, and sometimes cough. The next step is to deconstruct the airway into components of fixed and variable airflow obstruction, inflammation, infection and altered cough reflex, setting the airway disease in the context of extra-pulmonary co-morbidities and social and environmental factors. The emphasis is always on delineating treatable traits, including variable airflow obstruction caused by airway smooth muscle constriction (treated with short- and long-acting β-2 agonists), eosinophilic airway inflammation (treated with inhaled corticosteroids) and chronic bacterial infection (treated with antibiotics with benefit if it is driving the disease). It is also important not to over-treat the untreatable, such as fixed airflow obstruction. These can all be determined using simple, non-invasive tests such as spirometry before and after acute administration of a bronchodilator (reversible airflow obstruction); peripheral blood eosinophil count, induced sputum, exhaled nitric oxide (airway eosinophilia); and sputum or cough swab culture (bacterial infection). Additionally, the pathophysiology of risk domains must be considered: these are risk of an asthma attack, risk of poor airway growth, and in pre-school children, risk of progression to eosinophilic school age asthma. Phenotyping the airway will allow more precise diagnosis and targeted treatment, but it is important to move to endotypes, especially in the era of increasing numbers of biologicals. Advances in -omics technology allow delineation of pathways, which will be

particularly important in TH2 low eosinophilic asthma, and also pauci-inflammatory disease. It is very important to appreciate the difficulties of cluster analysis; a patient may have eosinophilic airway disease because of a steroid resistant endotype, because of non-adherence to basic treatment, and a surge in environmental allergen burden. Sophisticated –omics approaches will be reviewed in this manuscript, but currently they are not being used in clinical practice. However, even while they are being evaluated, management of the asthmas can and should be improved by considering the pathophysiologies of the different airway diseases lumped under that umbrella term, using simple, non-invasive tests which are readily available, and treating accordingly. Keywords: biomarker, transcriptomics, bronchial biopsy, bronchial brushings, induced sputum, airway inflammation, asthma phenotype, endotype

A phenotype is defined as the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment. It is important to make the distinction between phenotyping which is of clinical value (changes treatment, prognostic value) from those determining mechanistic pathways. However, if phenotyping does not help in either domain, it cannot be said to be useful. An endotype is defined as a subtype of a condition, which is defined by a distinct functional or pathobiological mechanism.

Airway Inflammation, and the Potentially Treatable Trait of Airway Eosinophilia. Airway Eosinophilia ICS are amongst the most effective agents in the whole of therapeutics for the vast majority of children with eosinophilic asthma. Low dose treatment, if taken efficiently and regularly, will result in complete control of asthma in most children , while accepting there are steroid resistant phenotypes. The most direct evidence of airway eosinophilia is of course obtained at fibreoptic bronchoscopy (FOB) with broncho-alveolar lavage (BAL) and endobronchial biopsy. This is of course not ethical or practical in most children, and non-invasive methods must be used. Induced sputum was initially the most popular technique, and although this is time-consuming, it is perfectly feasible as a diagnostic test for infection even in resource poor areas . Although in older children sputum and BAL eosinophilia are tightly correlated, this is not the case in pre-schoolers. Furthermore, there is a failure rate of up to 20%, and induced sputum does not reflect mucosal inflammation. Of the other non-invasive methods, peripheral blood eosinophil count has become most popular. It reflects BAL eosinophilia, and, even more importantly, is an excellent biomarker predicting response to anti-TH2 monoclonal antibody strategies. Peripheral blood eosinophil count can be measured on a finger prick sample with point of care equipment. Significantly, in the first attempt at personalized medicine in pre-school children, the combination of a peripheral blood eosinophil count >300/μλ and aeroallergen sensitization was the strongest predictor of response to ICS. Exhaled nitric oxide (FeNO) has also been used as a surrogate for airway eosinophilia. The utility of this method in reducing asthma attacks has been demonstrated, but although there is a relationship with induced sputum eosinophil count, it varies between individuals and is inconsistent in the same individual over time. Clearly FeNO and induced sputum are complimentary and useful, but exactly how they should be used in combination is unclear. However, the presence of airway eosinophils should prompt critical thought. Firstly, airway eosinophilia, although often related to inflammation, is not synonymous with that endotype, and this needs to be borne in mind when contemplating anti-TH2 monoclonal therapies. In our cohort of severe, therapy resistant asthmatics, those with steroid resistant airway eosinophilia had very little evidence of ongoing secretion of the signature TH2 cytokines interleukin (IL)- 4, IL-5 and IL-13, in either induced sputum supernatant, BAL or immunohistochemistry of endobronchial biopsy. Also, the U-BIOPRED group, using sputum transcriptomics in adult asthmatics documented a group which included patients with moderate sputum eosinophilia, who instead of having the expected TH2 handprint, were characterized by genes of metabolic pathways, ubiquitination and mitochondrial function, as well as, in another study, an IL-6 modulated pathway (below). Furthermore, if eosinophils are present in the airway, their role or otherwise

in disease causation should be carefully considered. In adults at least, eosinophilic bronchitis is a cause of chronic cough, but with no evidence of reversible airflow obstruction; treatment is with ICS, but not β-2 agonists. In a challenging study, airway biopsies were compared in patients with active asthma, normal controls, and patients who by any criteria had outgrown their previously diagnosed asthma. The airway wall histology, in terms of eosinophilia and reticular basement membrane thickness was the same irrespective of whether the patient had active asthma or had "outgrown" the disease. This leads to the challenging question as to what is the "X-factor" that is needed to convert airway eosinophilia into airway disease? At the moment this remains completely unknown. Having said all this, clearly if there is no airway eosinophilia, it seems to make little sense to prescribe an anti-eosinophil strategy such as ICS. Although it is true that corticosteroids have numerous genomic and non-genomic effects which hypothetically could be beneficial in airway disease, this has never been shown, and there may be potentially adverse effects in at least some airway diseases, for example reducing neutrophil apoptosis and prolonging the survival of this cell in the airway. Surely in the twenty-first century we should not prescribe anti-eosinophilic medications if there is no airway eosinophilia to treat, any more than anti-hypertensives should be prescribed to people who have a normal blood pressure? Neutrophilic Asthma? This is another area which illustrates the danger of extrapolating adult studies to children. Asthma characterized by mucosal and sputum neutrophilia is well described in adults, who tend also to have severe asthma with less evidence of atopy. Unsurprisingly, neutrophilic asthma is steroid non-responsive. By contrast, in our cohort of children with severe asthma, multiple atopic sensitization was common, but there was no evidence of mucosal, sputum or BAL neutrophilia. However, in a subgroup of patients neutrophils were found within the epithelium, and, quite unlike what might be expected from adult data, these patient had better symptom control (Asthma control test, ACT) and better first second forced expired volume while being prescribed a lower dose of ICS. Although it is always dangerous to move from cross-sectional associations to hypotheses, nonetheless it would seem that, whatever the role of neutrophils in adult asthma, in pediatric asthma neutrophils are having a beneficial effect. This raises the intriguing possibility that bacterial infection may have a role in some pediatric asthmas. Again highly speculatively, is it possible that excessively high doses of ICS might actually worsen "bacterial asthma" (if it exists!) by causing topical mucosal immunosuppression, leading to a positive feedback loop of worsening symptoms leading to higher ICS doses leading to worsening symptoms? Further data are needed to explore this. However, a practical clinical message is that the finding of BAL or mucosal neutrophilia should prompt a search for another diagnosis.

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