

Inflammatory biomarkers in severe asthma
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Asthma – more than inflammation - the airways in asthma undergo remodelling

Asthma is a complex disease

Scale bar 100 µm.

Heterogeneous disease requires multiple biomarkers for accurate diagnosis
 Wadsworth A et al. J Asthma Allergy 2011; 4: 77-86

Pros and cons of some currently used asthma biomarkers
 Adapted from Wadsworth A et al. J Asthma Allergy 2011; 4: 77-86

Biomarker	Advantage	Disadvantage
Pulmonary function e.g. spirometry, PEF, BHR	Non-invasive, sensitive, well validated	Unable to detect sub-phenotypes, reflect disease mechanisms or predict treatment responses
Tissue biopsy	Definitive measure of airway pathology	Highly invasive, require expertise
Induced sputum	Less invasive, reflects airway inflammation, useful to monitor CS treatment	Somewhat uncomfortable, requires expertise, reproducibility variable, difficult in children
Exhaled NO (eNO)	Non invasive, simple measurement technique, Highly sensitive to CS	A subset of asthma, care to standardise

Links between pathologic mechanisms and clinical consequences in asthma.
 Bousquet J et al. Am J Respir Crit Care Med. 2000;161:1720-45

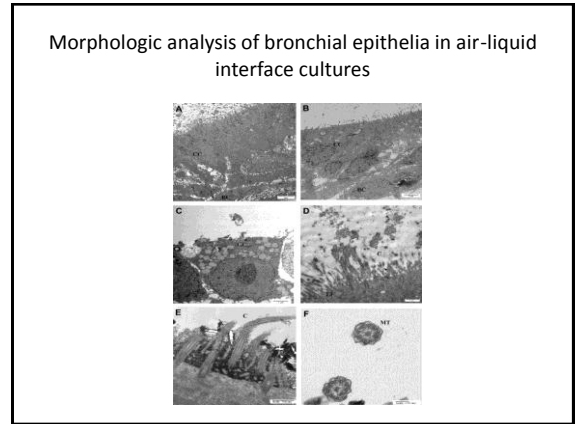
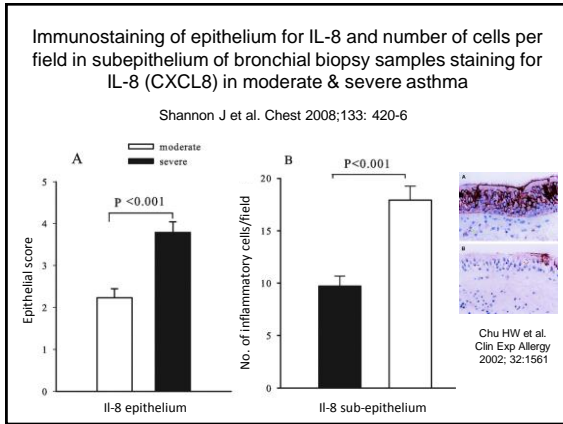
Sputum and circulating eosinophils are accepted as biomarkers of asthma, but lack discrimination for subphenotyping beyond "Th2 high" and "Th2 low"

Symptoms (broncho-constriction) Exacerbations nonspecific hyperreactivity Persistent airflow obstruction

Sputum eosinophils as a reliable biomarker of subtypes of severe asthma

Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. Green RH. et al Lancet. 2002; 360: 1715-21

Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Pavord ID. et al Lancet. 2012; 380: 651-9



An ex vivo model of severe asthma using reconstituted human bronchial epithelium

Gras D et al. J Allergy Clin Immunol. 2012;129:1259-66

➤ Human bronchial epithelial cells derived from bronchial biopsy specimens in mild and severe asthma cultured for 21 days in an air-liquid interface to form a fully differentiated airway epithelium.

Intrinsic abnormality in the epithelium to adopt a chronic wound and pro-inflammatory phenotype

- Greater levels of mucin secretion
- Released more CXCL8
- Produced lower levels of lipoxin A(4)
- Higher expression of gene for 15-lipoxygenase 2

Some alternative sources of biomarkers

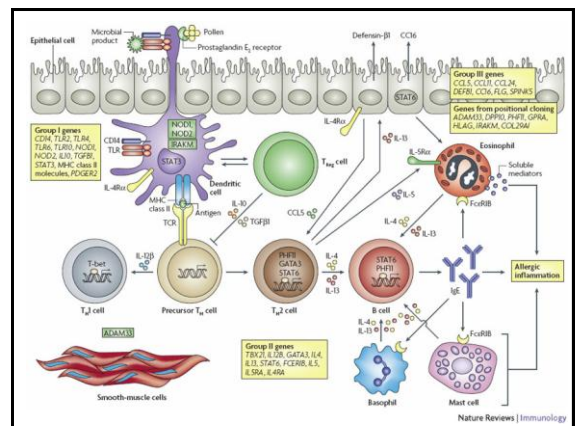
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Biomarker	Advantage	Disadvantage
Exhaled breath condensate & exhaled volatiles	Non-invasive, multiple biomarkers to enable subphenotyping	Highly variable, limited to small MW analytes, salivary contamination (EB)
Serum or plasma proteins	Less invasive, multiple biomarkers, standardised operating procedures established	Less airway specific, reflects subtle changes within circulating compartment
Urinary metabolites (>70)	Non-invasive, multiple biomarkers, SOPs established, good sensitivity but variable specificity	Unproven clinical use, limited access to analytical equipment e.g. NMR, MS

Application of metabolomics in asthma is becoming a reality

Can circulating inflammatory biomarkers help?

- Asthma severity in childhood and metabolomic profiling of breath condensate. ... et al. Allergy. 2013; 68: 110-7.
- Allergic asthma breath metabolome: a challenge for comprehensive two-dimensional gas chromatography. Caldeira M et al. J Chromatogr A. 2014; 1277-97.
- The metabolomics of asthma: diagnostic potential. Adamko DJ et al. Chest. 2012; 141: 1295-300.
- Allergic asthmatics show divergent metabolite profiles from healthy controls both at baseline and following allergen provocation. Lundström SL et al. PLoS One. 2012; 7: e33000.
- Metabolomic approach with LC-MS reveals significant effect of pressure on diver's plasma. Ciborowski M et al. J Proteomics. 2010; 9: 4131-7.
- Alterations of the arginine metabolome in asthma. Lara A et al. Respir Crit Care Med. 2008; 178: 673-81.



Immunological biomarkers in sera correlated with asthma control and quality of life measurements from chronic asthmatic patients.

Patil SP et al. Ann Allergy Asthma Immunol. 2011; 106: 205-13

- Sera from moderate and severe persistent asthma and normal controls
- 50 analytes, including cytokines, chemokines, angiogenic, and growth factors determined by multiplex assay.
 - > 12 of 29 cytokines higher in patients with asthma than controls, but only IFN γ significantly lower in asthma than controls. (IL)-3 and IL-18 levels were significantly higher in poorly controlled disease.
 - > 5 of 12 chemokines higher in patients with asthma than controls.
 - > 5 of 6 growth factors higher in patients with asthma than controls, and 3 were higher in those poorly controlled.
- IL-18, FGF2, HGF, and SCF correlated with poor asthma control and reduced quality of life

The application of proteomics

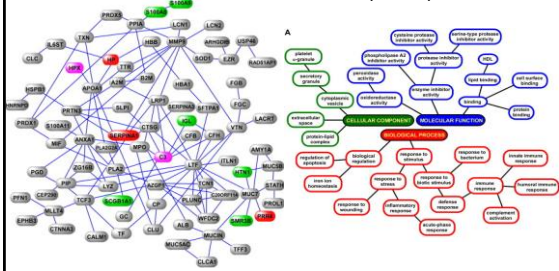
- Plasma proteomics can discriminate isolated early from dual responses in asthmatic individuals undergoing an allergen inhalation challenge. Singh A et al. Proteomics Clin Appl. 2012; 6: 476-85.
- Proteomics in asthma and COPD phenotypes and endotypes for biomarker discovery and improved understanding of disease entities. O'Neil SE et al. J Proteomics. 2011 ; 75: 192-201.
- Network analysis of quantitative proteomics on asthmatic bronchi: effects of inhaled glucocorticoid treatment. O'Neil SE et al. Respir Res. 2011; 12: 124.
- Induced sputum proteome in healthy subjects and asthmatic patients. Gharib SA et al. J Allergy Clin Immunol. 2011; 128: 1176-84

Proteomic pathway analysis to define different asthma endotypes: "molecular taxonomy"

Gharib SA et al. J Allergy Clin Immunol. 2011; 128: 1176-84

Asthma sputum interactome

Functional analysis of the sputum proteome



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Novartis
 GlaxoSmithKline
 AstraZeneca
 Chiesi
 Pfizer
 Roche
 UCB
 Boehringer Ingelheim
 Johnson & Johnson
 Almirall



Netherlands Asthma Foundation
 Asthma UK
 European Lung Foundation
 EFA
 Int Primary Care Respir Group
 Lega Italiano Anti Fumo

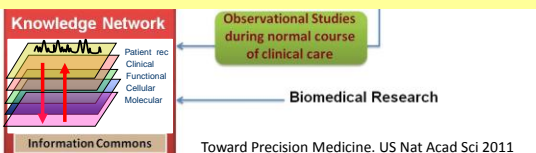
Biosci
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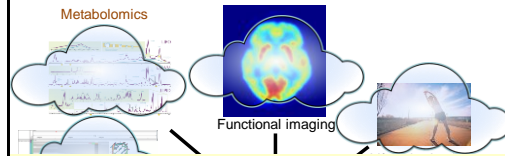
Creation of a New Taxonomy requires an "Information Commons" in which data on large populations of patients become broadly available for research use and a "Knowledge Network" that adds value to these data by highlighting their inter-connectedness and integrating them with evolving knowledge of fundamental biological processes.



Towards personalised medicine: reclassification of human disease by identifiable causal pathways



Metabolomics



The key to the success of stratified or personalised medicine will be the integration of complex data sets from multiple sources and the development of multidisciplinary research

