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Induced sputum continues to be used as a valuable technique in airways disease research, and infectious disease diagnostics.

Airways Disease

Inhaled corticosteroids effectively treat eosinophilic airway inflammation in asthma and COPD. Ernst et al. re-reviewed the efficacy and safety of inhaled corticosteroid (ICS) use in COPD [Ernst]. They identified a reduction in exacerbations with ICS use, but at the cost of a significant increase in adverse effects, particularly pneumonia. This emphasises the need for a way to predict response to ICS in COPD. They concluded that eosinophilic bronchitis (induced sputum eosinophils >3%) continues to be the most reliable predictor of a response to corticosteroids, but also commented that ‘there is an urgent need for better markers of benefit and risk that can be tested in randomised trials for use in routine specialist practice [Ernst].

Consequently a number of studies have been performed to identify simpler ways to detect airway eosinophilia. Blood eosinophils appear a very promising alternative. Korevaar et al. performed a systematic review and meta-analysis of 32 studies that evaluated simpler methods to detect sputum eosinophilia [Korevaar]. They found that most studies (80%) had risk of bias in one domain. The summary estimates of sensitivity and specificity of blood eosinophils for detecting sputum eosinophils of 3% or more in adults were 0.71 (0.65-0.76) and 0.77 (0.70-0.83), which was considered only moderately useful for clinical practice. However, studies in focussed populations, with less risk of bias, have also been reported, showing more promising results. Wagener et al. evaluated blood eosinophils, exhaled nitric oxide, and serum periostin for their ability to detect sputum eosinophilia in symptomatic asthma. They studied the markers in 2 separate populations, an initial diagnostic evaluation group, followed by a validation group. The results showed good predictive value of blood eosinophils with area under the curve values of 89% and 85% in the 2 populations respectively [Wagener]. Similarly, Fowler et al. found blood eosinophils a good predictor of sputum eosinophilia in severe asthma [Fowler]. The optimal cut-off point for blood eosinophils is around 0.3x10E9/L, which interestingly is within the reported normal range [usually >0.5x10E9/L]. Serum periostin was also been evaluated, as it is a marker of Th2 activation, however it had mixed results [Fowler], possibly because of the increasingly recognised pattern of non-TH2 mediated airway eosinophilia.

The finding that blood eosinophils can identify sputum eosinophilia in symptomatic asthma is a major advance that will facilitate stratified therapy in many clinical settings.

References


Wagener AH, de Nijs SB, Lutter R, Sousa AR, Weersink EJ, Bel EH, Sterk PJ. External validation of blood eosinophils, FE(NO)
Mechanisms of Airway Disease

Human airway challenge models have been essential in drug development in asthma. For example, the allergen challenge model has been used to evaluate many novel agents for eosinophilic and allergic asthma prior to clinical efficacy trials. Induced sputum forms a key outcome assessment in these models. With the recognition of noneosinophilic asthma as an important and common airway disease phenotype, there has been a need to develop a model of noneosinophilic airway inflammation. The inhaled endotoxin (lipopolysaccharide, LPS) model has now been developed and tested as a way to investigate noneosinophilic forms of asthma and COPD. Endotoxin is a cell wall component of gram negative bacteria, and is a potent stimulus of innate immune responses and neutrophilia. In this model, subjects inhale a dose of endotoxin in a controlled fashion, and this elicits a neutrophilic airway inflammatory response [Gupta]. Induced sputum provides the main outcome measure for the model. The model was tested in patients with COPD and was well tolerated, with a maximum mean change in FEV1 of 12% after 5μg LPS. The total sputum cell count and neutrophil count significantly increased 6 and 24 hours post LPS. There was an accompanying systemic response with increases in IL-6, CRP and CC-16, as well as increased in CD4+ and CD8+ cell associated IL-17 significantly increased at 4 hours [Gupta]. This demonstrates some useful features of the model, where it elicits some of the key inflammatory components of COPD.

The LPS model can also be used to test the effects of pharmacological inhibition of the non-eosinophilic airway response. Michel et al. studied healthy volunteers and showed that a TNF antagonist (adalimumab) inhibited the endotoxin-induced neutrophil influx, reducing induced sputum neutrophil counts from 51.3 (±6.4)% to 26.2 (±5.3)%, whereas oral corticosteroid had no effect on this response.

IL1β is now identified as a key mediator in neutrophilic airway diseases. Whole genome RNA expression studies with network analysis identify the IL1β pathway as a key active component on neutrophilic asthma, with IL1β forming a nodal point [Baines]. Hernandez et al. used the inhaled LPS model to test the effects of blocking IL1 with anakinra. This agent was initially trialled in inflammatory joint disease. They conducted a phase I double-blind, placebo-controlled crossover study in 17 healthy volunteers who received 2 daily subcutaneous doses of 1 mg/kg anakinra or saline (placebo), then one hour after the second dose, the subjects underwent an inhaled LPS challenge. Induced sputum was assessed for neutrophils at 4 hours post challenge. The investigators found that anakinra significantly reduced airway neutrophilia as well as IL-1β, IL-6, and IL-8 levels. They concluded that anakinra is a potential therapeutic candidate for treatment of neutrophilic asthma.

Further clinical validation of the relevance of the model was provided by McSharry et al. who identified elevated endotoxin in asthmatic sputum, and that those patients with higher sputum endotoxin levels had an im-
paired lung function response to oral. This suggests that the endotoxin model could be an early predictor of clinical efficacy of novel therapeutics.

References


Tuberculosis and Diagnostics

Tuberculosis diagnostics has undergone a major technological advance with the use of molecular diagnostics in combination induced sputum. The Xpert MTB/RIF testing system uses the PCR reaction to detect MTB DNA in sputum samples. The test is quality controlled and allows more rapid diagnosis [Chew]. Induced sputum provides a reliable means to obtain airway samples for testing, and induced sputum combined with Xpert MTB/RIF testing has been found to be feasible and accurate in remote settings, as well as primary care settings [Ugarte-Gil]. It is curious that induced sputum can be feasible for infectious disease diagnosis yet considered too difficult for the diagnosis of eosinophilic bronchitis. The key difference may be the availability of a companion molecular diagnostic to pair with the induced sputum sampling. This is now possible in asthma with the identification of a 6-gene signature that predicts inflammatory phenotype in asthma [Baines].

References


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