The role of CFTR mutations in asthma

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The role of the causative gene for cystic fibrosis (CF) in other respiratory disorders has been investigated for many years, even before the CF transmembrane conductance regulator (CFTR) was discovered. CF, asthma and chronic obstructive pulmonary disease (COPD) are all characterized by a chronic inflammatory state, airway remodelling and exacerbations due to respiratory tract infections. While there are many differences between these diseases, there are sufficient commonalities to justify the investigation of CFTR genetic variants as playing a role in asthma and COPD.

Atopy (1), asthma (2) and bronchial hyper-responsiveness (3) have all been associated with heterozygosity for CF mutations, suggesting overlap in the pathogenic mechanisms underlying CF and asthma/allergies. In contrast, Schroeder et al (4) found evidence that heterozygosity for the ∆F508 mutation was protective against asthma; however, other studies (5-7) have found no association. Dahl et al (8,9) reported that heterozygosity for ∆F508 was associated with increased risk of asthma and, among asthmatic patients, was associated with lower lung function. The cytokine profile in CF patients is dominated by Th2 cytokines characteristic of asthmatic patients, although it has been shown that Th2 is the predominant response in CF patients with chronic Pseudomonas aeruginosa infection (11).

Associations between ∆F508 (and other CFTR mutations) and diffuse bronchiectasis have also been reported (12-14). In addition, ∆F508 was shown to be associated with chronic bronchitis (15), but subsequent studies did not confirm this finding (13,16). Chronic colonization of the airways by bacteria is an important mechanism of disease progression in COPD (17), suggesting similarities between CF and COPD. However, the literature regarding the role of CFTR variants in COPD is conflicting (18-21). Most recently, genome-wide association studies of lung function (22-25), COPD (26,27), emphysema (28) and asthma (29-31) have not identified CFTR as a susceptibility gene.

In the current issue of the Canadian Respiratory Journal, Goodwin et al (32) (pages 46-48) present a case series of four patients with asthma and recurrent neutrophilic bronchitis. All of the patients had sweat chloride levels within the normal range and did not have two copies of known CF-causing mutations. The results of this case study suggest that CFTR gene variants play a role in this subtype of asthma. It is possible that the reason for the confusion in the previous literature regarding CFTR mutations and asthma is at least partially due to the extent of phenotyping of the patients – associations with CFTR mutations may be more evident in specific subsets of asthmatic patients such as those with neutrophilic disease. The authors also showed that hypertonic saline may be a useful therapy in such cases.

The link between CFTR and asthma suggested in the study by Goodwin et al is intriguing, but not yet proven. The presence of non-CF-causing sequence variants (ie, polymorphisms) in case #3 is difficult to interpret because such variants are common and likely to have modest, if any, effect on the function of the CFTR. The role of mutations that cause CF is more compelling; three of four patients were heterozygous for one known CF-causing mutation, whereas approximately 4% of the general Caucasian population would be expected to carry carriers. Nevertheless, the results must be viewed with caution due to the small sample size, and a larger study with equally well phenotyped patients would be needed to resolve this issue.

REFERENCES
