Novel use of the lysosomal enzyme acid ceramidase for the treatment of inflammatory lung diseases, including cystic fibrosis

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Abstract: Previous studies have shown that sphingolipid abnormalities occur in the lungs of patients and animals with cystic fibrosis (CF) and other inflammatory lung diseases. Among these abnormalities are elevated ceramide, which contributes to inflammation and lung cell death, and reduced sphingosine, which contributes to enhanced infectivity. Herein we determined ceramide and sphingosine levels in broncholavage fluid (BALF) and/or sputum of CF patients, and correlated the findings with clinical status and age. We also evaluated the use of inhaled recombinant acid ceramidase (rhAC) to correct the sphingolipid imbalance in CF mice, patient sputum and cells. The protein rhAC is a lysosomal enzyme currently being manufactured for the treatment of acid ceramidase deficiency disorders, Farber disease and spinal muscular atrophy with myoclonic epilepsy. BALF was obtained from 24 CF and 17 non-CF pediatric patients with lung disease (disease controls), age 0.3 to 20 years. BALF from 5 healthy (non-smoking) adult controls, age 35–56 years, also were obtained. Sputum was obtained from 8 adult CF patients, age 25 to 52 years. In the pediatric BALF samples, positive correlations of ceramide with age were found in both the CF and disease control populations. Of note, pediatric CF patients had significantly higher ceramide levels than healthy adult controls (p = 0.013). A strong inverse correlation (r = −0.78) was also observed between sputum sphingosine and age in the adult CF patients. These results are consistent with previous findings showing the stimulation of pathways that enhance ceramide production in CF (e.g., activation of acid sphingomyelinase), as well as the reduction of acid ceramidase activity leading to reduced sphingosine. Based on these findings we also evaluated the therapeutic potential of rhAC. A single inhalation of rhAC into the lungs of CF mice reduced ceramide, elevated sphingosine, and prevented infection with Pseudomonas aeruginosa. The rhAC treatment of CF patient sputum and cells also corrected the sphingolipid imbalance. Studies are currently planning to evaluate the effects of repeated rhAC administration in the context of chronic inflammation and infection CF models, and to study the potential of rhAC in other models of lung disease (e.g., acute lung injury, COPD).