Infection and Inflammation MUC up the Cystic Fibrosis Airway

The predominant feature of cystic fibrosis (CF) is muco-obstructive lung disease. Loss of or deficiency of cystic fibrosis transmembrane receptor (CFTR) activity results in decreased chloride and bicarbonate secretion and increased apical cell membrane sodium absorption via dysregulation of the epithelial sodium channel. The result is a compressed periciliary liquid layer leading to mucociliary stasis, which in turn, promotes the so-called vicious cycle of chronic airway infection and inflammation.

The focus of investigations into mucus obstruction in cystic fibrosis has largely been on the direct effects of CFTR dysfunction on airway mucus properties such mucus hyper-concentration and abnormal viscoelasticity, and not on how the CF vicious cycle itself can alter airway mucus in CF. This is not only very relevant but important, as CF airway mucus really is a complex mixture, with the constituent foreign pathogens, airway mucins, respiratory epithelial and inflammatory cells and cell products all interacting with and affecting each other. In a study reported in this issue of the *Journal*, Batson and colleagues (pp. 253–265) describe their findings related to CF airway mucins in the context of microbiome–mucus interactions and high protease environment (1).

The key observations in this study are that the major gel-forming mucins, MUC5AC and MUC5B, are increased in the CF airway compared with non–CF healthy controls, consistent with the previous literature. The authors found that the total mucin increase as well as MUC5AC and MUC5B correlated with both age of the patient as well as sputum neutrophil elastase activity. The natural history of CF lung disease is marked by repeated episodes of robust infection and inflammation termed pulmonary exacerbations. Surprisingly, the authors did not find changes in mucin amounts comparing samples obtained during clinical stability with those during a pulmonary exacerbation. Several years ago, we published a longitudinal study looking at CF sputum rheology in relation to pulmonary function, and also changes in sputum rheology during CF pulmonary exacerbation (2). We found that sputum viscoelasticity increased during pulmonary exacerbation and returned to baseline with clinical recovery. In retrospect, taking the findings in Batson and colleagues into consideration, this suggests that the increased viscoelasticity we saw during CF pulmonary exacerbation was due to increased extracellular DNA, which is consistent with the findings of increased NETosis during CF pulmonary exacerbation.

Additionally, the ratio of MUC5AC to MUC5B was also increased in the CF airway compared with non–CF healthy controls, which appears to be a hallmark across the muco-obstructive disease spectrum (3). MUC5AC is also thought to form more viscoelastic gels than MUC5B (4), which as the authors referenced is consistent with this observation. Increased MUC5AC/MUC5B ratio is also seen in asthma and is thought to be correlated with type-2 inflammation (5) and in fatal asthma exacerbations patients are thought to develop acute respiratory failure from highly tenacious mucus plugs (6). Likewise, the authors also found that in non–CF bronchiectasis patients compared with control subjects, total mucins as well as MUC5AC and MUC5B were increased similarly as seen in CF suggesting that inflammation is a major unifying driving force across the spectrum of muco-obstructive disease.

Despite the dramatic increases in total mucins and in gel forming mucins, and the highly proteolytic environment in the CF airway, the authors surprisingly found that the mucins were not degraded. This is different from what others have reported (7). The authors also show that despite the highly oxidative environment in the CF airway the radius of gyration of CF mucins was similar to non–CF healthy control subjects, implying that intermolecular forces such as disulfide bond cross-linking is unlikely in CF. These results are in contrast to a 2015 paper by Yuan and colleagues, in which the authors found that CF mucus was more viscoelastic than non–CF control mucus (8). Yuan and colleagues deduced that this increased "stiffness" in CF mucus was due to increased oxidation in the CF airway, as evidenced by the observation of reducing agents decreasing the viscoelasticity of CF mucus to that of non–CF controls and oxidation of non–CF control mucus recapitulating the increased viscoelasticity of CF mucus. The authors then found via mass spectrometry analyses of CF sputum evidence for increased CF mucin cross-linking through increased post-translational halogenation of tyrosine residues. However, Batson and colleagues failed to find evidence of mucin cross-linking that these post-translational modifications would suggest.

Lastly, using a glycomic analysis of CF and non–CF control mucins in conjunction with microbiome analysis, the authors found that CF mucins were both more sialylated and less sulfated and that these changes were due to the airway microbiome and host immune responses. Nonetheless, while these pathogen and host immune cell effects do not alter mucins in muco-obstructive diseases, degradation of airway mucins provides substrates for bacterial growth, further perpetuating the infection–inflammation cycles in these diseases.

This is an innovative study providing insight into the pathophysiology of muco-obstructive diseases. As is customary, such novel studies have a tendency to generate more questions than answers, particularly when data contrast with similar published work. ■

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