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MINI-SYMPOSIUM: AIRWAY CLEARANCE IN CYSTIC FIBROSIS

Mucus structure and properties in cystic fibrosis

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Summary The biophysical properties of airway secretions are largely determined by the polymeric components. In normal airway mucus, the gel-forming mucins, MUC5AC and MUC5B, are responsible not only for the viscoelastic properties essential for clearance and protecting the airway epithelium from invaders and water evaporation. With chronic airway infection, inflammatory cell necrosis leads to a predominance of polymeric DNA and F-actin. There is almost no mucin in the sputum of patients with established cystic fibrosis lung disease. Sputum viscoelastic and surface properties determine how well secretions can be cleared by cilia or cough. In this mini-Symposium on Airway Clearance in Cystic Fibrosis, the physiology of CF secretion structure and rheology is discussed in the context of medications and physical maneuvers for enhancing sputum clearance.

INTRODUCTION

Since the first description of cystic fibrosis (CF) more than 50 years ago, it has been known that these patients eventually succumb to severe lung disease associated with chronic infection. In persons with CF, there is extensive and progressive bronchiectasis associated with accumulation of large amounts of purulent secretions. This toxic soup of pro-inflammatory cytokines, neutrophil breakdown products and bacteria leads to progressive damage to the airways and lungs. Promoting airway clearance using a variety of medications and chest physical therapy or airway clearance techniques and devices has long been a mainstay of CF therapy.[1,2]

Clinical wisdom has suggested that patients with CF have thick secretions in their airway that make it difficult to clear bacteria, and that this promotes the development of bronchiectasis. This hypothesis of abnormal airway mucus was based, in part, on recognition of the severe bowel obstruction due to inspissation of abnormal meconium. However, studies going back more than 25 years have shown that CF sputum is neither thick nor viscous when compared to mucus from patients with chronic bronchitis or asthma.[3–5] Although it is true that the more purulent (a marker of neutrophil necrosis) secretions are, the more viscous they become,[3] CF sputum viscosity is less than that of other diseases that are not as relentlessly progressive.

A very attractive hypothesis is that CFTR dysfunction leads to low water and low salt content of airway surface fluid, presumably increasing mucin concentration.[6] Depletion of the periciliary liquid layer can decrease both mucociliary and cough transportability.[7] It has also been hypothesized that mucus dehydration leads to increased mucin concentration and, in association with decreased mucin pH, decreased reduced glutathione and increased myeloperoxidase, this leads to the formation of additional inter-chain mucin bonds. These extra cross links increase viscoelasticity leading to poor mucus clearance and persistent infection.[8] Increased mucin concentration has been shown to hinder neutrophil migration and promote hypoxemic conditions in sputum, leading to bacterial biofilm morphologic transformation.[9]

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SECRETION PROPERTIES

The biophysical properties of airway secretions include rheology, cohesivity and surface properties such as adhesivity and tenacity. The rheologic properties of a material describe how the material responds to an applied stress.[10] When stress is applied to a solid material, it stores energy and this stored energy is released when the stress is removed. The storage modulus or elastic deformation is characteristic of solids and an ideal solid has a Hookian, or pure elastic, response. An ideal, or Newtonian, liquid responds to a stress by deforming and flowing as long as stress is applied. The energy is lost to this system through the action of flow, and the rate of flow with the applied stress, or the stress/strain response, is the loss or viscous modulus. Pseudoplastic substances like gels initially store energy like a solid and then begin to deform as the application of stress continues. Thus, a gel behaves like both a liquid and a solid. Isolated measurements of viscosity can be misleading when applied to a gel. Both viscosity and elasticity are important for mucus clearance. When mucus is extruded from the submucous gland, it must spread across the airway epithelium; this means that liquid-like deformation must progress and there must also be a decrease in surface tension to allow the mucus to spread.[11] For cilia effectively to propel mucus there must be storage of the kinetic energy from beating cilia in the mucus and this stored energy is then translated into the motion of the mucus sheet upon recoil. Restitution of viscoelasticity prevents the mucus from falling back down along the airway tube with gravity. Thus, in model systems, increasing viscosity will improve cough clearability.[12]

The properties associated with the surface interaction of the mucus with the epithelium and with airflow are just as important as viscoelasticity for secretion clearance.[13] Surface interactions include wettability or how well the mucus can spread at the air–liquid–solid interface as measured by the contact angle; interfacial tension (called surface tension for a Newtonian liquid); adhesivity, which is the surface force at the interface between a solid and a liquid; and tenacity which is the product of adhesive work and cohesivity.[14] Cohesivity, or the attraction of like molecules, is related to polymer length and polymer density.[15,16] Adhesive properties are especially important in cough clearance because the more secretions adhere to the epithelium, the more difficult they are to clear by cough. It has been shown that although CF secretions are not exceptionally viscous (Table 1), they are highly adhesive, and this combination of high adhesivity and low viscosity makes cough clearance difficult in CF. Sputum mucociliary and cough transportability is dramatically increased by decreasing the adhesive work of secretions and activating surfactant phospholipids; the latter is a major therapeutic effective dornase alfa (Pulmozyme, Genentech, S. San Francisco, CA).[17]

Mucus properties can be measured in a variety of ways. Measurements, such as timing how quickly mucus pours from a container or pourability, how well it compacts in a tube after centrifugation (compactability), or the wet and dry weight of expectorated sputum, are simple to perform but are not precise or reproducible, nor do they provide meaningful data about the biophysical properties of secretions or how these properties are affected by medications.

Dynamic viscoelasticity measures the strain response of mucus to an applied stress. Because mucus is subjected to both low stress (ciliary beat) and high stress (cough) conditions, we measure the strain developed in response to a dynamic stress. Interfacial tension (called surface tension for liquids) is the force at the gel–air interface. This is a component of the adhesive work and is measured by the de Nouy platinum ring technique.[14] Cohesivity is the attractive force between like molecules and this is defined as interfacial tension multiplied by the new area created after a test substance is pulled apart. For ideal or Newtonian fluids this equals 2× the interfacial tension, γ.[15] Wettability indicates the ability of a liquid or gel to spread on a surface. It is measured using computer analysis of the contact angle, θ, formed by a sessile drop at the air–gel–solid interface. Tenacity is the product of cohesivity and adhesive work, the latter defined by the Laplace equation for the work of adhesion:[13]

$$\mathrm{Wad} = \gamma(1 + \cos\ \theta)$$

Table 1 The viscosity of CF sputum is less than that of bronchitis or asthma secretions although viscosity is greater in more purulent sputum for all of these diseases. (Reproduced from Lopez-Vidriero and Reid.[3])

	Sputum viscosity (poise at 1350 s^{-1})		
	Mucoid	Mucopurulent	Purulent
Chronic bronchitis	0.41 (0.08–1.25)	0.61 (0.15–1.63)	1.07 (0.46–1.38)
Bronchiectasis		0.39 (0.07–0.89)	0.61* (0.21–1.63)
Cystic fibrosis	0.25 (0.04–0.46)	0.39 (0.16–0.84)	0.84 (0.39–1.60)
Asthma	0.56 (0.09–1.72)	1.46* (0.26–3.10)	

* However studies going back more than 25 years have shown that CF sputum is neither thick nor viscous when compared to mucus from patients with chronic bronchitis or asthma.