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Review

Cystic fibrosis: An inherited disease affecting mucin-producing organs☆

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ABSTRACT

Our current understanding of cystic fibrosis (CF) has revealed that the biophysical properties of mucus play a considerable role in the pathogenesis of the disease in view of the fact that most mucus-producing organs are affected in CF patients. In this review, we discuss the potential causal relationship between altered cystic fibrosis transmembrane conductance regulator (CFTR) function and the production of mucus with abnormal biophysical properties in the intestine and lungs, highlighting what has been learned from cell cultures and animal models that mimic CF pathogenesis. A similar cascade of events, including mucus obstruction, infection and inflammation, is common to all epithelia affected by impaired surface hydration. Hence, the main structural components of mucus, namely the polymeric, gel-forming mucins, are critical to the onset of the disease. Defective CFTR leads to epithelial surface dehydration, altered pH/electrolyte composition and mucin concentration. Further, it can influence mucin transition from the intracellular to extracellular environment, potentially resulting in aberrant mucus gel formation. While defective HCO_3^- production has long been identified as a feature of CF, it has only recently been considered as a key player in the transition phase of mucins. We conclude by examining the influence of mucins on the biophysical properties of CF sputum and discuss existing and novel therapies aimed at removing mucus from the lungs.

This article is part of a Directed Issue entitled: Cystic Fibrosis: From o-mics to cell biology, physiology, and therapeutic advances.

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1. Introduction

CF is the most common genetic disease, occurring prevalently in the Caucasian population at a rate of 1 in 2500 newborns of Northern European descent. The most common symptoms of CF include progressive lung disease and chronic digestive conditions, which are the result of mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) (Riordan et al., 1989). Depending on genetic and environmental factors, symptom severity varies among individuals carrying CFTR mutations. More specifically, CF pathogenesis is characterised by the build-up of thick, sticky mucus in multiple mucin-producing organs, such as the lungs, sinuses, intestine, pancreas and reproductive organs. For this reason, CF is also known as mucoviscidosis, suggesting that polymeric, gel-forming mucins, the large O-linked glycoproteins responsible for the viscoelastic properties of mucus, play a critical role in the disease (Kreda et al., 2012).

Since the discovery of the defective CF gene in 1989, almost 2000 mutations have been reported and are available in the Cystic Fibrosis Mutation Database.[1] The CFTR gene encodes for a cyclic adenosine monophosphate (cAMP) regulated chloride channel expressed in apical membranes of various epithelia (Gregory et al., 1990). In addition to controlling chloride secretion, this channel regulates the function of other membrane proteins, including the epithelial sodium channel (ENaC) (Briel et al., 1998). Both CFTR and ENaC play an important role in maintaining homeostasis by controlling the movement of water through the epithelium, which is particularly important for mucous membranes. Hence, CFTR malfunction leads to fluid hyperabsorption and subsequent dehydration of the epithelial surface, which, in turn, results in abnormal mucus gel with an increased polymeric mucin concentration and altered biophysical properties (Boucher, 2007; Button et al., 2012).

Among other tissues, CFTR is expressed in the pancreas, intestine, lungs, and reproductive tract, and each organ-specific phenotype can be related to the production of aberrant mucus with altered biophysical properties (Burgel et al., 2007; Malmberg et al., 2006; Reid et al., 1997). Common symptoms exhibited in mucin-producing organs are blocked ducts and impaired mucosal defence. In this review, we focus on the role of CFTR in the intestine and lungs since these organs have been the subjects of most studies involving the biophysical properties of mucins. By controlling fluid secretion and regulating ion composition in these organs, CFTR plays a critical role in mucosal defence by modulating the biophysical properties of mucus and assisting in bacterial killing (Norkina et al., 2004a; Pezzulo et al., 2012; Puchelle et al., 2002). Abnormal modulation of epithelial inflammation related to CFTR malfunction may further contribute to CF pathophysiology, but the link has yet to be established. CFTR also plays an important role in the transcellular secretion of bicarbonate (HCO_3^-), an alkalizing agent that plays a crucial physiological role in pH buffering. Although impaired bicarbonate secretion was reported early in the discovery of the disease (Hadorn et al., 1968), the role of this anion in CF has only recently been a major focus of interest within the mucus/mucin community. As highlighted by Quinton (2008), CF individuals suffer from complications in all mucin-secreting organs, which may be a consequence of defective HCO_3^- transport. Consistent with this idea, reduced HCO_3^- secretion in CF may be responsible for lowered epithelial surface pH, which has been shown to impede bacterial killing (Pezzulo et al., 2012) and increase mucus/mucin viscoelasticity (Celli et al., 2005; Georgiades et al., 2013). More specifically, there is emerging evidence that HCO_3^- plays a key role in the expansion of polymeric mucins after their secretion into the extracellular milieu that is essential for normal mucus gel formation and transport (Chen et al., 2010; Cooper et al., 2013).

Before the use of physiotherapy (to remove mucus from the lungs) and enzyme therapy (e.g., pancreatic enzymes to correct digestive enzyme insufficiency and inhaled DNase treatment to alter mucus properties), CF was considered to be a fatal childhood disease. However, with improved therapies and strategies for managing the disease, the average life expectancy for CF patients is now 37 years.[2] In recent years, small molecule therapies directed at restoring CFTR functionality have yielded success with a small number of mutations and are being pursued for other, more common mutations. Indeed, the goal of developing CFTR-specific therapies for all patients is currently a key objective of the Cystic Fibrosis Foundation. In the meantime, alternative approaches are being investigated (e.g., the use of mucolytics, inhibitors of mucin secretion and osmotic agents) to address the problem of mucus accumulation/obstruction in CF patients. In this article, we will review the current understanding of mucus and mucins in CF, describe how inefficient post-secretory mucin expansion may result in mucus with aberrant physical properties, and conclude by discussing therapies aimed at removing mucus from the lungs.

2. Consequences of CFTR mutations for mucus

The molecular mechanisms by which CFTR mutations can disrupt CFTR function include defects in protein synthesis (class I), maturation/trafficking (class II, e.g., ΔF508, the most common mutation with nearly 90% of patients carrying at least one allele), channel gating (class III, e.g. G551D, the target of Kalydeco; see Section 4), altered conductance (class IV) and decreased CFTR abundance (class V) (Ferec and Cutting, 2012). As mentioned above, these defects lead to deficient cAMP-dependent Cl^- and HCO_3^- secretion and enhanced ENaC-mediated Na^+ absorption in affected epithelia, resulting in dehydration of the mucus and concentration of its components (e.g., mucins) (Boucher, 2007). As a result, the majority of CF patients require a daily routine of inhaled therapies and exercise to prevent the progression of lung disease or a decrease in lung function. Additionally, most CF patients suffer from gastrointestinal (GI) manifestations regardless of their genotype. A similar pathogenesis cascade of obstruction, infection and inflammation is observed in the airways and intestines and is thought to be the direct result of epithelial surface dehydration and abnormal electrolyte composition.

2.1. Changes in mucus properties in the intestine

Expression of the CFTR gene in the GI tract is low in the stomach and rises in the intestine, displaying a gradient with the highest mRNA levels in the duodenum and lowest levels in the large intestine (Strong et al., 1994). This pattern of expression may reflect the need for acid neutralisation via HCO_3^- secretion as the proximal intestine receives a highly acidic bolus from the stomach. In addition to exhibiting high levels of CFTR expression, the normal intestine receives large volumes of HCO_3^--rich material from the pancreas. Proper pH buffering and fluid secretion in the intestine is essential for the optimal functioning of digestive enzymes and the maintenance of normal bacterial flora. In the case of CF, the combination of prolonged acidity following food uptake and dehydrated intestinal mucus facilitates bacterial growth in the GI tract (De Lisle and Borowitz, 2013; Fridge et al., 2007; Lisowska et al., 2009). Mucus adhesion to the intestinal wall may be related to mucin

[1] http://www.genet.sickkids.on.ca/cftr/ConsortiumDataPage1.html.

[2] http://www.CFF.org.

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