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Mucin Secretion in Cystic Fibrosis: A Systematic Review

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Keywords
Cystic fibrosis · Mucin · MUC5AC · MUC5B

Abstract
Background: Mucus protects the epithelium against invaders and toxic materials. Sticky and thick mucus is characteristic of CF. ***Objective:*** The aim of this systematic review is to characterize the specific mucins secreted in the lung and intestinal tract of CF patients. ***Methods:*** A systematic literature search was conducted up to December 31, 2019. The following terms were used: "cystic fibrosis" AND "mucin." Case-control studies comparing mucin expression in CF patients to healthy controls were included. ***Results:*** We found 741 eligible studies, 694 studies were rejected because they were performed in animals and not in full text, and 32 studies were excluded being editorials, duplications, review articles, meta-analysis, or not in English. Fifteen studies were eligible for our study, including 150 CF patients compared to 82 healthy controls, all fulfilled the inclusion criteria. The main mucin types expressed in the sinus submucosal glands, sputum, tracheobronchial surface epithelium, and lung submucosal glands were MUC5AC and MUC5B. Increase in the number of sinusoidal submucosal glands and expression of MUC5B was found in CF patients, but no such difference from healthy controls was found for the number of goblet cells in the surface epithelium nor in the expression of MUC5AC. The opposite was found in the tracheobronchial surface epithelium and in the lungs. ***Conclusions:*** Increased expression of MUC5AC in the surface epithelium and of MUC5B in the subepithelial glands may be the result of higher secretion rate of mucin into the lumen of the respiratory tract, causing mucus plaque, infection, and inflammation.

Introduction

Mucus layers cover epithelial surfaces in the respiratory and gastrointestinal tracts and protect the epithelium against invaders and toxic materials [1]. The main components of the mucus layer are mucins, high-molecular weight, heavily glycosylated O-linked glycoproteins, which are synthesized by the epithelium, and composed of 2 types: secreted and membrane bound [2]. More than 20 mucin genes exist in the human genome. Secretory mucins are secreted by goblet cells and contribute to a thin layer over the mucosal surfaces, while membrane-bound mucins are attached to the mucosa and also involved in cell signaling, immune modulation, cell motil-

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ity, adhesion, and growth [2, 3]. MUC5AC and MUC5B are the main mucins secreted in the lung, MUC5AC and MUC6 in the stomach, and MUC2 in the small intestine and the colon [4, 5]. Change in mucin synthesis, secretion, or degradation may be a primary event or secondary to inflammation, infection, or carcinogenesis.

Cystic fibrosis (CF), a common genetic disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), is characterized by progressive lung disease and digestive organ pathology [6]. Sticky and thick mucus covering the epithelial surface of the bronchial tree, sinuses, pancreatic ducts, intestinal tract, and the reproductive tract is the main characteristic of CF [7]. Intestinal obstruction is often associated with CF, particularly the meconium ileus that affects 15% of CF newborns. Thick mucus blocks pancreatic ducts and results in pancreatic destruction during the second and third trimester of gestation.

CFTR regulates chloride secretion, the function of epithelial sodium channel, and bicarbonate transport, controlling the movement of water. Dehydration of the mucosal surfaces when CFTR is mutated results in changes of the mucin properties in all organs and tissues mentioned, leading to obstruction, infection, and inflammation with the signs and symptoms of the disease.

Analyzing MUC5AC and MUC6 in CF lung sputum revealed contradictory results. Henke et al. [6] demonstrated decreased concentration, while Kirkham et al. [7] found overproduction, especially in exacerbations. Similarly, the data on other organs' mucin secretion in CF are sparse and controversial. Montserrat et al. [8] demonstrated high mucin secretion from normal pancreatic cells provoked by extracellular ATP, but not from CF pancreatic cells. In both, ATP induced a rapid intracellular calcium mobilization. Thus, CFTR seemed to mediate ATP-dependent mucin secretion.

The aim of this systematic review is to characterize the specific mucins secreted in the lungs and intestinal tract of CF patients. Understanding better the pathogenesis of CF may facilitate development of new therapies, elongate survival, or prevent organ transplantation.

Methods

Literature Search

A systematic literature search was conducted of English language publications in MEDLINE, PubMed, Scopus, EMBASE, and CENTRAL, up to December 31, 2019. The following terms were used: "cystic fibrosis" AND "mucin." Relevant studies were screened according to established protocol. In addition, the references of reviews were screened, and studies added when appropriate (Fig. 1).

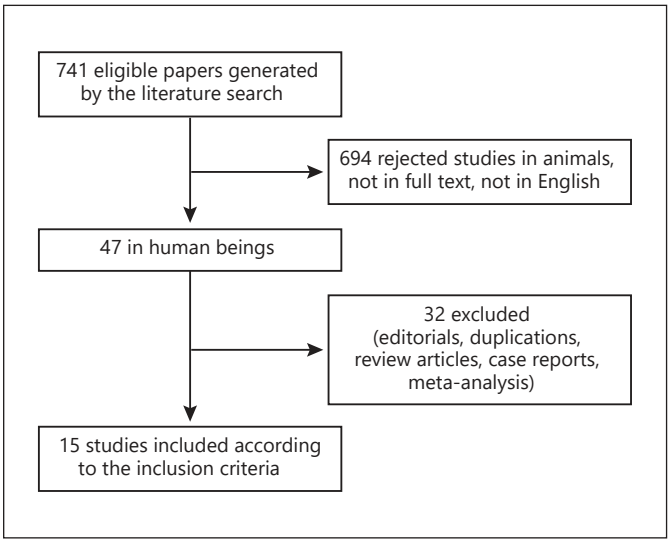

Fig. 1. Studies selected to the systematic review. Mucin secretion in CF. CF, cystic fibrosis.

Inclusion and Exclusion Criteria – Study Selection and Data Extraction

Case-control studies comparing mucin expression in CF patients to healthy controls were included. Mucin expression in the nasal mucosal surface, tracheobronchial mucosa, intestinal tract epithelium, pancreatic ducts mucosa, submucosal glands of the lung and sinuses, and the sputum was studied. Mucin expression studies included several different physical and chemical methods: purification by gel filtration chromatography, cesium chloride analytical gradient ultracentrifugation, protease treatment and disulfide bond reduction, in situ hybridization and immunocytochemistry for different MUCs mRNA and protein, mRNA slot-blot (Northern blot), ELISA, Western blot after agarose gel electrophoresis, beta-elimination of O-linked oligosaccharides, and analysis by single-ion chromatography, comparing glycosylation.

Results

We found 741 eligible studies, 694 studies were rejected because they were performed in animals and not in full text, and 32 studies were excluded being editorials, duplications, review articles, meta-analysis, or not in English. Fifteen studies were found eligible, including 150 CF patients compared to 82 healthy controls from 5 countries (USA, Canada, Germany, Sweden, and UK) that fulfilled the inclusion criteria, published till December 31, 2019 (Fig. 1; Table 1) [9–23].

Table 1. Mucin secretion in CF

Author	Country	Data set	Mucin secreted
Wesley et al. [9]	Canada	Human intestinal mucins from 6 patients with CF and 8 controls were prepared from tissue obtained at surgery and postmortem Cesium chloride analytical gradient ultracentrifugation and carbohydrate side chains were examined	CF mucin was denser and more highly glycosylated than of controls and contained more sulfate The increase in glycosylation resulted from a rise in fucose, galactose, and N-acetylglucosamine
Rose et al. [10]	USA	Tracheobronchial mucins from 2 healthy individuals and from 3 patients with CF Mucins were purified on Sepharose 4B and 2B columns, and their chemical and physical properties compared	Normal mucins required a dissociating and a reducing agent for solubilization. CF mucin was smaller than normal mucin due to intensive degradation
Gupta and Jentoft [11]	USA	Tracheobronchial mucin samples from 2 controls and 6 CF patients. Mucins were purified by gel filtration chromatography and by density-gradient centrifugation. Protease treatment and disulfide bond reduction performed	Normal secretions contained higher molecular weight mucins than CF secretions There was no change after treatment
Li et al. [12]	UK	Nasal mucosa of 12 CF patients and 4 controls In situ hybridization for mRNA of MUC2	Expression was higher in the nasal mucosa of CF patients than in healthy controls
Reid et al. [13]	USA	Expression in the material obstructing pancreatic ducts of 6 fetuses, 2 normal children, and 2 CF patients In situ hybridization and immunocytochemistry for MUC6 mRNA and protein, respectively	MUC6 mucin is a significant constituent of the material obstructing the small pancreatic ducts in CF
Harris and Reid [14]	UK	DNA from 50 CF patients DNA for MUC6 tandem repeat length with Southern blot	No change in MUC6 tandem repeat length in CF patients with or without pancreatic insufficiency was found
Voynow et al. [15]	USA	Noninflamed nasal epithelial cells of 14 CF patients, 6 patients with allergic rhinitis and 12 controls. mRNA slot-blot (Northern blot) for MUC1, MUC2, MUC5AC	No change in CF patients versus controls for MUC1 and MUC2 A significant decrease of MUC5AC expression in CF patients
Davies et al. [16]	Sweden	Sputum of 5 CF patients Immunochemistry, ELISA, and density-gradient centrifugation in CsCl	MUC5AC and MUC5B were detected with only 5% MUC2 in the gel phase. More MUC5AC in the sol phase due to higher degradation rate
Groneberg et al. [17]	UK	Surface epithelium of the trachea and bronchi from 6 CF patients and 3 controls Immunohistochemistry to MUC5AC and MUCB comparing CF patients with healthy control	Increased goblet cell numbers positive to MUC5AC in the surface epithelium of the trachea and bronchi No change in MUC5B staining in the subepithelial glands
Kirkham et al. [7, 18]	UK	Sputum of 10 CF, 9 COPD patients, and 15 healthy controls Western blot after agarose gel electrophoresis	Increased expression of MUC5B in CF and COPD
Schulz et al. [19]	Germany	Secretions from lung submucosal glands of 5 CF patients compared to 5 patients with other lung diseases and 3 healthy controls Beta-elimination of O-linked oligosaccharides and analysis by single-ion chromatography, comparing glycosylation of MUC5AC and MUCB	No difference in glycosylation was demonstrated
Henke et al. [20]	Germany	Sputum of 11 CF patients in remission and exacerbation of the lung disease, 12 healthy controls Western blot for MUC5AC and MUC5B	Decreased expression in CF patients of MUC5AC (89%) and MUC5B (40%) than control Increased expression in exacerbation
Guo et al. [21]	USA	DNA of CF patients with different disease severity Southern blot and PCR measurement of MUC5AC	Association between VNTR length of MUC5AC and lung disease severity
Wu et al. [22]	USA	Sinus mucosa of 21 CF children and 18 normal controls Immunohistochemistry	×4.4 increased submucosal glands, with increased expression of MUC5B. No change in MUC5AC nor in goblet cells number
Henderson et al. [23]	USA	Sputum collected from 10 CF and 13 healthy subjects, and from HBE cell culture Size exclusion chromatography and differential refractometry techniques	Increased MUC5AC (×4.5) and MUC5B (×2.6) Increase in the number of goblet cells

CF, cystic fibrosis.

Study Description

Wesley et al. [9] studied human intestinal mucins from 6 patients with CF and 8 controls which were prepared from tissue obtained at surgery and postmortem. Cesium chloride analytical gradient ultracentrifugation and carbohydrate side chains were examined. CF intestinal mucin was denser and more highly glycosylated than of controls and contained more sulfate. The increase in glycosylation resulted from a rise in fucose, galactose, and N-acetylglucosamine.

Rose et al. [10] studied tracheobronchial mucins from healthy individuals and from patients with CF, which were isolated from lung mucus, purified, and their chemical and physical properties compared. Normal mucins required a dissociating and a reducing agent for solubilization. CF mucin was smaller than normal mucin due to intensive degradation.

Gupta and Jentoft [11] collected tracheobronchial mucin samples from controls and CF patients and purified them by gel filtration chromatography and by density-gradient centrifugation. Protease treatment and disulfide bond reduction were performed. Normal secretions contained higher molecular weight mucins than CF secretions. There was no change between CF patients and controls after protease treatment and disulfide bond reduction, and the same subunits of 2,000 and 300 kDa were released. Thus, the main difference between CF patients and controls was a more effective process of degradation of mucin in the CF patients.

Li et al. [12] found that the MUC2 gene is expressed at 3- to 4-fold higher levels in CF nasal mucosa than in non-CF nasal mucosa and submucosal mucus-secreting glands. Reid et al. [13] demonstrated MUC6 expression in the material obstructing pancreatic duct of CF patients. They looked at mRNA (in situ hybridization) and the protein (immunocytochemistry). They also found similar distribution of MUC6 and CFTR in the pancreatic tissue.

Harris and Reid [14] could not demonstrate any change in MUC6 tandem repeat length between CF patients and controls. Voynow et al. [15] found a significant decrease in MUC5AC expression, using mRNA slot-blot (Northern blot), in the nasal mucosal epithelial cells of CF patients versus controls. No difference was demonstrated in the expression of MUC1 and MUC2.

Davies et al. [16] found high concentration of MUC5AC and MUC5B in the sputum of 5 CF patients, using immunochemistry and density-gradient centrifugation in CsCl. In the sol phase, also small molecules that were the result of MUC5AC degradation were found. MUC2 was as a component of the insoluble residue from the gel, which accounted for <4% by mass of the total mucins.

Groneberg et al. [17] found similar immunohistological staining to MUC5AC and MUCB in CF patients and healthy control, but hyperplasia of surface epithelial goblet cells was positive for MUC5AC in CF patients' trachea and bronchi. Kirkham et al. [18] found increased expression of MUC5B in CF and COPD patients in comparison with healthy controls. They used Western blot of sputum after agarose gel electrophoresis.

Schulz et al. [19] could not find any difference in glycosylation of MUC5AC or MUCB in the submucosal glands of airways in CF patients when compared with other lung diseases or healthy controls. They used beta-elimination of O-linked oligosaccharides and analysis by single-ion chromatography.

Henke et al. [20] compared MUC5AC and MUC5B protein expression in 11 CF patients with lung disease remission and exacerbation and 12 healthy controls. A decrease of 89% in MUC5AC and of 40% in MUC5B was found in active CF patients in comparison with controls. An increase was demonstrated in exacerbation of the disease.

Guo et al. [21] found a significant association between MUC5AC variable number tandem repeat (VNTR) length and CF severity of lung involvement. Wu et al. [22] found a significant hyperplasia of submucosal glands of sinus mucosa in CF children, with an increased expression of MUC5B compared to normal controls. No change was demonstrated for goblet cells neither for MUC5AC expression.

Henderson et al. [23] were the first to demonstrate increase in mucin concentration of CF lung secretions using size exclusion chromatography and differential refractory techniques. They found 3-fold increase in MUC5B gene expression (measuring RNA) and 4.5- and 2.6-fold increases in MUC5AC and in MUC5B concentrations, respectively. Their findings contradicted those depended on immunochemistry which demonstrated the opposite. The explanation for the discrepancy may be that proteolytic degradation of the mucin backbone by specific enzymes caused disappearing of some antigenic sites. Increased mucin concentration caused increased osmotic pressure in the mucin layer, stasis, defective cilia, and cough-mediated mechanical clearance of bacteria, infection, and inflammation. The main mucin types expressed in the sinus submucosal glands, sputum, tracheobronchial surface epithelium, and lung submucosal glands were MUC5AC and MUC5B [16, 18, 22, 23] (Table 2).

Increase in the number of sinusoidal submucosal glands and in the expression of MUC5B was found in CF patients, but no such difference from healthy controls was found for

Table 2. Mucin characteristics in CF

Tissue or secretion	Mucin characteristics
Intestinal mucus	CF mucin was denser, more highly glycosylated, and contained more sulfate than intestinal mucin of controls The increased glycosylation added more fucose, galactose, and N-acetylglucosamine sugar residues to the mucin backbone of CF patients (Wesley et al. [9])
Pancreatic duct secretion	MUC6 is a significant constituent of the material obstructing the small pancreatic ducts in CF patients (Reid et al. [13])
Sinus submucosal glands	Increase in the number of submucosal glands and in the expression of MUC5B was found in CF patients versus healthy controls. No such difference was demonstrated for MUC5AC or the number of goblet cells (Wu et al. [21])
Nasal mucosa	MUC2 expression was higher in the nasal mucosa of CF patients than in healthy controls (Li et al., [12]) This observation could not be confirmed in uninflamed nasal epithelial cells for MUC1 and MUC2 (Voynow et al. [15])
Sputum	MUC5AC and MUC5B were the dominating mucins. More MUC5AC was found in the sol phase due to high degradation rate (Davies et al. [16]) Increased expression of MUC5B and MUC5AC was found in CF patients than in healthy controls but also in COPD patients; thus, it may be related to inflammation (Kirkham et al. [7, 18], Henderson et al, [23]) Decreased expression of MUC5AC and MUC5B in CF patients in clinical remission when compared to healthy controls but increased expression in exacerbation. Though inflammation may cause mucin hypersecretion
Tracheobronchial mucus	CF mucin was smaller than normal mucin due to intensive degradation, as shown in 2 studies (Rose et al. [10]; Gupta and Jentoft [11]) Normal mucin, but not CF mucin, required dissociation by a reducing agent for solubilization Increased goblet cell number, positive immunochemical staining for MUC5AC was demonstrated in the tracheobronchial surface epithelium (Groneberg et al. [17]) MUC5B staining was the same for CF patients and healthy controls
Lung submucosal glands	No difference in MUC5AC and MUCB glycosylation was demonstrated between CF patients and healthy controls (Schulz et al. [19])
DNA	No change in MUC6 tandem repeat length in CF patients, with and without pancreatic insufficiency, was found (Harris and Reid [14]) Association between tandem repeat length of MUC5AC and lung disease severity was demonstrated (Guo et al. [21])

CF, cystic fibrosis.

the number of goblet cells in the surface epithelium nor in the expression of MUC5AC [22]. The opposite was found in the tracheobronchial surface epithelium and in the lungs, increased goblet cell number with a positive immunochemical staining for MUC5AC [17]. No such increase was found in the lung submucosal glands or for MUC5B expression [19]. Since increased expression of MUC5AC and MUC5B was also demonstrated in sputum of COPD patients, this might be the result of inflammation [18, 23]. CF mucin of the tracheobronchial secretion was smaller than normal mucin due to intensive degradation, as shown in 2 studies [10, 11], in contrast with CF intestinal mucin which was denser, more highly glycosylated, and contained more sulfate than intestinal mucin of healthy controls [9].

Discussion

Although the pathophysiology of CF is related to the viscous and sticky mucus secreted by the epithelial surfaces of the respiratory and intestinal tracts, the interrelationship with nonfunctional CFTR is still unknown. Recently, it was found that CFTR is also able to transport bicarbonate, which is more linked to disease severity than the chloride secretion [24]. The reason for the lack of understanding the relation between CFTR and changes in mucin synthesis and secretion is the difficulty in studying the mucins. The main types of mucins involved in the etiopathogenesis of CF are gel-forming mucins MUC5B (synthesized in the submucosal glands) and MUC5AC

(synthesized from the surface goblet cells) [25]. These mucins are heavily glycosylated proteins that occur as polymers and have a long backbone, or core protein, and many O-linked carbohydrate side chains. VNTR characterizes mucin, composed of different numbers of amino acids (typical for every mucin) and rich in amino acids serine, threonine, and proline. Proteases have difficulties to cut the protein backbone at this area of VNTR, and the mucin is relatively difficult to degrade. Mucin units are attached by a sulfide bond to form a huge viscoelastic molecule. This enormous size protein with the dense glycosylation poses methodological difficulties to study and characterization.

Assessment of mucin expression is done by several physical and chemical methods, such as purification by gel filtration chromatography on Sepharose 4B or 2B, cesium chloride analytical gradient ultracentrifugation and carbohydrate side chain examination, protease treatment and disulfide bond reduction, in situ hybridization and immunocytochemistry for different MUCs mRNA and protein, mRNA slot-blot (Northern blot), ELISA, Western blot after agarose gel electrophoresis, beta-elimination of O-linked oligosaccharides and analysis by single-ion chromatography, comparing glycosylation, Southern blot, and PCR measurement of MUCs [26]. This richness of methods to measure mucin RNA or protein expression makes interpretation of many studies difficult and sometimes comparing results of studies which used different methods impossible.

Most of the studies found increased mucin expression, secretion, and concentration, followed by reactive increased enzymatic degradation [9–11, 15, 23] and elongation of VNTR that correlated with disease severity [21]. Wesley et al. [9] described increased mucin density and more sulfate residues – these may explain the higher density caused by creation of more disulfide bridges between the heavy molecular mucin subunits. Thus, we speculate that all these changes make the mucin of CF patients extremely viscous, increase stasis, form mucus plagues, and prevent cilia function and clearance of bacteria. In addition, other mucins than MUC5AC and MUC5B, such as MUC2 [12] and MUC6 [13], are overexpressed in the pancreatic tissue, with similar distribution as CFTR [13] which may explain pancreatic duct pathology.

The role of microbiome in CF etiopathogenesis is unknown. One approach used capillary tubes instilled with artificial sputum intended to mimic CF physiologic conditions, which were then inoculated with bacterial strains derived from patients with CF collected during periods of clinical stability and exacerbation [27]. The investigators observed increased gas production and a 2-unit reduction in pH before the onset of exacerbation. Theoretically, decrease in sputum pH may significantly increase mucin density.

Colorectal cancer incidence is higher in CF patients [28]. CFTR deficiency causes the mucus layers to become dehydrated and dysfunctional and permits bacterial contact with the epithelia. The inflammation may promote sequence of events that cause stem cell proliferation and colorectal cancer [28].

The results of the studies in our systematic review incline towards an important role for mucins in the etiopathogenesis of CF. Increased expression of MUC5AC in the surface epithelium and of MUC5B in the subepithelial glands may contribute to higher secretion rate of mucin into the lumen of the respiratory tract, causing mucus plaque, infection, and inflammation. Further studies should be conducted to explore the possible genetic or epigenetic changes in the mucin genes or the connection between CFTR mutation and mucin changes. A new era of management and treatment of CF will start with these studies, with new therapeutic options that will prevent lung transplantation or mortality.

Statement of Ethics

The research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yaron Niv: acquisition of data, analysis and interpretation of data, and drafting of the manuscript. Samuel B. Ho: acquisition of data, analysis, and interpretation of data. Theodor Rokkas: study concept and design, analysis and interpretation of data, and drafting of the manuscript.

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