Commentary

Unique presentations and chronic complications in adult cystic fibrosis: do they teach us anything about CFTR?

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Abstract

The increase in numbers of adults with cystic fibrosis (CF) has allowed us to identify previously unrecognized chronic complications of CF, as well as appreciate unique presentations of cystic fibrosis-related diseases. Do these chronic complications and unique presentations provide us with new insight into cystic fibrosis transmembrane conductance regulator (CFTR) function? Current data suggest that the 'chronic complications' reveal mainly the effect of a long-term absence of previously recognized CFTR functions. In contrast, the 'unique presentations' provide new insight into the role of CFTR in different tissues.

Keywords: congenital bilateral absence of the vas deferens, cystic fibrosis, cystic fibrosis transmembrane conductance regulator, malignancy, pancreatitis

Introduction

One of the most striking trends in cystic fibrosis (CF) over the past few decades has been the marked increase in expected life span, with median survival improving from less than 10 years in the 1960s to more than 30 years now. Currently more than one-third of all individuals with CF are over the age of 18 [1], and trends suggest that in the next decade adults will account for nearly half of the CF population. It is accepted that new insights into the basic pathophysiology of CF might allow continued increases in survival, but is the converse also true? Will increased survival allow greater insight into the basic pathophysiology of CF? This question can be asked because with increased length of survival has come the recognition of previously underappreciated CF-related complications including an increased risk of gastrointestinal and perhaps pancreatic malignancy, osteoporosis, and diabetes. Furthermore, greater attention to 'adult' CF has also led us to identify, with increased frequency, atypical presentations of dysfunction of cystic fibrosis transmembrane conductance regulator (CFTR): chronic pancreatitis, congenital bilateral absence of the vas deferens (CBAVD), chronic sinusitis, and allergic bronchopulmonary aspergillosis. Do these unique presentations and chronic complications of adult CF teach us anything about the function of CFTR?

Complications in adult CF

When deciding whether the complications of adult CF provide us with insight into CFTR function, the key question

CBAVD = congenital bilateral absence of the vas deferens; CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator.

to ask is: do these complications suggest previously unrecognized functions for CFTR, or are they due to the long-term absence of already recognized CFTR functions? A prime example of an area in which this question should be asked is the role of CFTR dysfunction in increasing the risk for malignancy. A study in 1995 by Neglia *et al* [2] on the risk of cancer in patients with CF revealed that although the overall risk for cancer is similar to that of the general population, there is an increased risk for digestive tract cancers. In particular, there is an increased risk for ileal and colonic adenocarcinoma. Similar results were found in an earlier study by Sheldon *et al* [3]. Other reports have suggested an association between CF and pancreatic adenocarcinoma [3,4]. The key question is: are these neoplasms related to previously unrecognized functions of CFTR, or are they secondary to chronic inflammation, infection, or malnutrition, which might predispose to malignancy?

At present there is no evidence that CFTR mutations are directly responsible for oncogenicity. To start with, when the data from Neglia *et al* [2] are examined more closely, only one of the 24 cases of malignancy identified occurred in a patient under 20 years of age. A similar trend is seen when reviewing reported cases of CF and pancreatic malignancy: none has occurred before the age of 25 [4–6]. If CFTR mutations were directly oncogenic, it is likely that malignancies would be seen more frequently early in life. In 1997, Padua *et al* attempted to look directly at the relationship between the ΔF508 mutation and malignancy by screening more than 1700 patients with one of six different common tumors including colon, breast, lymphoma, and leukemia, for the ΔF508 mutation. Not only was there not an increased frequency of ΔF508 presence in any of the malignancy groups compared with a control group, there was actually a lower than expected frequency in patients with colonic adenocarcinoma [7]. Until evidence to the contrary is found, it must be assumed that the increased risk of certain malignancies seen in CF is secondary not to previously unidentified roles of CFTR but to the long-term absence of already recognized CFTR functions. In gastrointestinal malignancy several mechanisms have been suggested, including a change in the functional environment of the small bowel owing to abnormal bile acid metabolism [3], chronic steatorrhea [3], and selenium and vitamin E deficiency [8].

Other common adult-onset CF complications include diabetes and osteoporosis. Again, it is unlikely that these complications suggest previously unrecognized roles for CFTR. CF-related diabetes develops on average at around 20 years of age in individuals with long-standing pancreatic exocrine insufficiency. It is known that CFTR has a key role in the ductal epithelium of the pancreas, and its dysfunction is thought to result in protein hyperconcentration, precipitation and obstruction within pancreatic ducts. The subsequent parenchymal damage is likely to contribute to the development of diabetes and has been documented in autopsy studies of CF-related diabetes: pancreatic ductal blockage and dilatation, fatty and fibrotic replacement of tissue, severe loss of β cells, and significant amyloid deposition [9,10]. Despite some evidence for alterations in insulin secretion independent of β cell destruction, there is currently insufficient evidence to propose new pancreatic roles for CFTR. Similarly, osteopenia/osteoporosis, which is present in 65% or more of adults with CF [11], is unlikely to provide great insight into CFTR. CFTR expression has not been documented in osteoblasts or osteoclasts. Studies suggest that bone disease in CF is probably multifactorial, owing to a combination of malnutrition (vitamin D and calcium) [12], circulating cytokines [13], inadequate androgens and estrogens [14], and exogenous use of glucocorticoids.

Unique presentations

In contrast with chronic complications, however, unique presentations of CFTR-related diseases in adults have provided significant insight into CFTR function. This has occurred in particular in isolated presentations of CFTR-related diseases such as CBAVD, chronic pancreatitis, and chronic sinusitis with nasal polyposis. All of these have helped to provide an understanding of the hierarchy of tissue sensitivity to CFTR dysfunction.

It is clear from these atypical presentations of CFTR dysfunction that it is the vas deferens, pancreas, and sinuses that are the tissues most sensitive to decreases in CFTR function. The sensitivity of the vas deferens was first recognized in adult men with CBAVD and otherwise non-CF phenotypes. A recent study of more than 800 men with isolated CBAVD found that 71% had two CFTR mutations [15]. Almost universally they had at least one Class IV or Class V CFTR mutation, which results in levels of CFTR function estimated to be about 10% of normal [16]. Women with similar mutations have been reported to have thick cervical mucus and hypofertility, suggesting a possible female equivalent to CBAVD that affects the paramesonephric ducts [17]. Because only a small portion of men with CBAVD have evidence of lung, sinus or pancreatic pathology, we must conclude that in general it is the mesonephric and paramesonephric ducts that are among the most sensitive tissues to CFTR dysfunction.

The more recently recognized entity of CFTR-related pancreatitis suggests that the pancreas is also particularly sensitive to CFTR dysfunction. A study by Cohn *et al* [18] screened a cohort of 27 patients with chronic idiopathic pancreatitis for 17 common CF mutations and the 5T allele in intron 8 of the gene for CFTR. Despite this limited screening, 37% of them had at least one CFTR mutation, and 11% had two identifiable CFTR mutations; 19% of the patients had the 5T allele in intron 8 of the gene for

CFTR, a mutation that permits the formation of a small amount of normal CFTR but causes the vast majority of CFTR transcripts to lack exon 9 and be dysfunctional. Only one of the patients had CBAVD and none had CF sinopulmonary disease. This suggests that, like the vas deferens, the pancreas is among the most sensitive tissues to CFTR dysfunction. The manifestation of CFTR dysfunction in the pancreas is determined by the degree of decrease in CFTR levels, with a decrease to 10% of normal leading to an increased risk for pancreatitis, and a decrease to levels less than 1% leading invariably to exocrine pancreatic insufficiency. Further research is needed to determine whether the CFTR deficiency leads directly to pancreatitis or whether it increases the risk of pancreatitis only after exposure to stressors [19].

The third group of patients that give us insight into tissue sensitivity to decreases in CFTR function are patients with chronic sinusitis and polyposis. The evidence is mounting that a moderate decrease in CFTR function can lead to isolated sinus disease. A recent study by Wang *et al* [20] found an increased frequency of CF mutations in patients with chronic sinusitis and otherwise non-CF phenotypes. Friedman *et al* [21] noted an association of the 5T allele with atypical sinopulmonary disease. In retrospect, some of the men initially studied and identified as having CFTR-related CBAVD were noted later to exhibit symptoms of sinus disease [22].

Conclusion

So, although adult CF complications such as colonic malignancy, diabetes, and osteoporosis have not provided significant new insights into CFTR function, the unique presentations of CF-related diseases in adults have done so. CBAVD, pancreatitis and sinus disease have given us a better understanding of the hierarchy of tissue sensitivity to CFTR dysfunction. In future the study of these disease presentations, as well as other unusual presentations of CFTR dysfunction such as allergic bronchopulmonary aspergillosis [23] and idiopathic disseminated brochiectasis [24], might lead to the identification of previously unidentified roles for CFTR.

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