

Emerging role of cystic fibrosis transmembrane conductance regulator - an epithelial chloride channel in gastrointestinal cancers

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Abstract

Cystic fibrosis transmembrane conductance regulator (CFTR), a glycoprotein with 1480 amino acids, has been well established as a chloride channel mainly expressed in the epithelial cells of various tissues and organs such as lungs, sweat glands, gastrointestinal system, and reproductive organs. Although defective CFTR leads to cystic fibrosis, a common genetic disorder in the Caucasian population, there is accumulating evidence that suggests a novel role of CFTR in various cancers, especially in gastroenterological cancers, such as pancreatic cancer and colon cancer. In this review, we summarize the emerging findings that link CFTR with various cancers, with focus on the association between CFTR defects and gastrointestinal cancers as well as the underlying mechanisms. Further study of CFTR in cancer biology may help pave a new way for the diagnosis and treatment of gastrointestinal cancers.

Key words: Gastrointestinal cancer; Protein interaction; Cystic fibrosis transmembrane conductance regulator; Nuclear factor κ B; Signaling molecule

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Core tip: The present review aimed to analyze most published data regarding the emerging role of cystic fibrosis transmembrane conductance regulator (CFTR), an epithelial chloride channel in many tissues and organs, in various cancers, with the focus on the link between CFTR dysfunction and gastrointestinal cancers. The possible underlying mechanisms have also been discussed.

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INTRODUCTION

Cystic fibrosis transmembrane conductance regulator (CFTR), a glycoprotein with 1480 amino acids, is a cAMP activated anion channel expressed in the epithelial cells of a wide variety of tissues including lung, pancreas, liver, sweat gland, reproductive system, and intestine^[1,2]. Mutations or dysregulation of CFTR will cause several pathological conditions such as cystic fibrosis (CF), a common life threatening autosomal recessive disease in the Caucasian population^[3]. The *CFTR* gene, identified in 1989, is approximately 230kb containing 27 exons^[4]. CFTR protein contains 12 hydrophobic membrane-spanning regions, 2 cytoplasmic nucleotide binding domains (NBD) involved in ATP binding and hydrolysis, and one cytosolic regulatory domain which can be phosphorylated by PKA and PKC^[5,6]. Even though it was identified initially as a chloride channel, other functions of CFTR have also been characterized over the past decades. CFTR performs as a modulator of other ion channels and transporters^[7-10], and it can also cooperate with other proteins by forming macromolecular complexes to regulate important cellular processes^[11-14]. Recently, it has been reported that CFTR is likely to interfere with the expression of proteins involved in the signaling pathways of inflammation^[15,16]. Additionally, it has been reported that CFTR is associated with apoptosis in proximal renal failure^[17]. Therefore, the defect in CFTR function results in multi-system disorders affecting airways, pancreatic ducts, bile ducts, intestines^[18,19].

Accumulating research has demonstrated that aberrant expression or function of CFTR may lead to various pathological conditions, especially inflammatory diseases and inflammation-associated cancers^[20-22]. Recently, a large cohort study which recruited 41188 cases of CF patients conducted in the United States revealed an elevated risk of digestive tract cancers among CF patients^[23]. In addition, another group also reported an increased risk of malignancies for the kidney, thyroid, endocrine, lymphoma, skin and prostate in CF patients^[23]. Moreover, some groups showed that the *CFTR* gene is hypermethylated in several cancer cell lines and resected tumors^[22,24-26], which indicates that defects in the expression or function of CFTR may have a pivotal role in the pathogenesis of various cancers. It has also been well established that CFTR is critical in maintaining epithelial cell polarity and integrity^[27]. Consequently, the observed association between cancer risk and CFTR, as well as the connection between CFTR and cell junction molecules, has led to the hypothesis that CFTR plays important roles in cancer progression^[28,29]. In this review, we focus on the recent findings that associate CFTR with various cancers, especially gastrointestinal cancers.

CFTR AND GASTROINTESTINAL CANCER

Focus has been placed on the association between pancreatic cancer risk and CFTR deficiency since the early 1990s^[30] when cohort studies were performed to investigate how CFTR variants affect the risk of pancreatic cancer^[31,32]. CF patients suffer from chronic pancreatic damage and inflammation, which may predispose them to malignancy^[33]. Even though the overall cancer risk in CF patients is similar to that of the general population, CF patients are at elevated risk (6.5 fold) of developing gastrointestinal cancers including pancreatic cancer^[32]. The results from the cohort studies indicate an increased risk for pancreatic cancer among CF patients, which is supported by two recent reports^[33,34], in which multiple CFTR mutations were analyzed. These studies also found that patients who are CFTR mutant carriers develop pancreatic cancer earlier than those who carry normal CFTR. While there are reports that do not support the view that CFTR mutations increase the risk of pancreatic cancer^[35,36], Maisonneuve *et al.*^[23] concluded that there is a consistent increased risk of pancreatic cancer in CF patients, which is supported by retrospective studies that recruited a large amount of cases and screened multiple CFTR mutations^[33,34]. The difference between the reported associations of pancreatic risk and CFTR variation could be due to multiple reasons such as limited case number, different parameters regarding selection of the control population, mutations investigated in the study, and environmental factors including smoking and alcohol consumption. This requires regional or even global collaboration to adjust the possible biases that could occur as a result of the mentioned parameters^[37].

Different interpretations have been presented by investigators based on the observations of epidemiological studies and laboratory research to reveal the underlying mechanism of the association between CFTR and cancer. One mechanism is that CFTR dysfunction in the exocrine pancreas results in an ion transport defect, giving rise to obstruction of the pancreatic duct and consequently chronic inflammation, which is closely related with cancer initiation^[34]. It has been reported that wild-type CFTR suppresses tumor progression by negatively regulating MUC4, a protein involved in tumor growth and metastasis, providing a potential mechanism for CFTR inhibiting pancreatic cancer progression^[38]. Another group reported that increased PKC activity is associated with degradation of CFTR in pancreatic ductal cells^[39]. Altogether, these studies indicate that the microenvironment and cell signaling change in tumor cells could be implicated in the down-regulation of CFTR expression and the up-regulation of certain cancer promoting proteins in pancreatic cancer.

There is an increased risk of gastrointestinal cancers in CF patients, of which colon cancer is the most prevalent^[32]. Case reports have described CF patients developing colon cancer at relatively young ages^[40-42]; meanwhile, the mechanism behind this phenomenon has also been investigated, and several speculations have been

proposed. According to reports from different groups, Ras, PKC and interferon-gamma (IFN- γ) are involved in the down-regulation of CFTR in colonic ductal cells^[39,43-45]. More interestingly, the down-regulation of CFTR is correlated with drug resistance in colon cancer^[46]. When HT-29 cells, a human colorectal adenocarcinoma cell line, were treated with an increasing amount of colchicine, an alkaloid with anti-cancer activity^[47], the down-regulation of CFTR was accompanied by the acquisition of a drug resistant phenotype, and the restored expression of CFTR was observed when the drug was removed^[46]. Although the mechanism is not fully understood, it is possible that CFTR may transport certain unidentified metabolites or factors other than ions. Recently, Sun *et al.*^[48] demonstrated that the interaction between CFTR and AF-6/afadin, an adherens junction molecule, is important in the process of colon cancer migration and metastasis. In their study, the expression of CFTR and the interaction between CFTR and afadin were linked to epithelial-mesenchymal transition (EMT), an important process during tumor metastasis, indicating that functional CFTR may act as a tumor suppressor, while the deficiency of CFTR would facilitate tumor progression in colon cancer^[48].

The involvement of CFTR deficiency was also studied in other gastrointestinal malignancies such as gastric cancer^[49]. It is reported that serum CFTR is significantly associated with a cancer biomarker, carbohydrate antigen 199 (CA199), and it is significantly associated with gastric cancer staging. In addition, the combination of CFTR and CA199 yields a higher receiver operating characteristic (ROC) curve, which is used in the diagnosis of gastric cancer^[49]. Although this research did not discuss the association between CFTR and gastric cancer, it has provided a potential biomarker for the diagnosis of not only gastric cancer but also other types of cancer.

CFTR AND OTHER CANCERS

A large cohort study conducted by Neglia *et al.*^[32] demonstrated that the genetic variation of the CFTR gene is associated with a moderate increase (1.4 fold) in the risk of lung cancer, and CFTR gene mutation has been reported in lung cancer patients^[50,51]. Epigenetic modifications such as DNA methylation regulate gene expression to maintain cell growth and development. However, aberrant DNA methylation of the cytosine preceding guanosine (CpG) sites of the promoter regions of many genes plays a critical role in cancer by silencing the tumor suppressor genes, which is one of the earliest alternations in cancer^[52,53]. Hypermethylation of the CFTR promoter gene has been reported, and corresponding clinical data also indicates that CFTR promoter gene hypermethylation is associated with significantly poorer survival among younger lung cancer patients^[22]. On the other hand, CFTR gene expression was restored when A549 cells, a human lung adenocarcinoma epithelial cell line, were treated with demethylation reagents^[22]. Similarly, the results of a retrospective study from another group demonstrated that low CFTR expression is correlated with advanced stage

and metastasis as well as poor prognosis in non-small cell lung cancer^[54]. Similar to the findings in colon cancer^[48], investigators linked the expression of CFTR to EMT in lung cancer and demonstrated that CFTR suppresses EMT *via* inhibiting the uPA/uPAR-mediated signaling pathway^[54]. These findings indicate that functional CFTR may play an inhibitory role in the initiation and progression of lung cancer.

Based on the results obtained from different groups, the protective role of CFTR on tumor progression is reflected by the inhibitory effect on tumor metastasis, which seems unrelated to its ion transportation activity. It has been reported that CFTR physically interacts with multiple proteins including ZO-1^[55], E-cadherin^[56], multidrug resistance protein-2 (MRP2)^[14], MRP4^[13], and afadin^[48]. These protein-protein interactions may be important in the inhibition of tumorigenesis. On the other hand, functional CFTR has been shown to down-regulate tumor promoting proteins such as NF- κ B, which plays a pivotal role in inflammation and cancer progression^[57].

The role of CFTR has also been examined in the pathogenesis of other cancers such as prostate cancer^[24,58], hepatocellular cancer^[26,59] as well as bladder^[25] cancer with the focus mainly on DNA methylation. CFTR promoters are hypermethylated in these cancers compared with normal tissues. Moreover, researchers proposed that it is possible that methylation of the CFTR promoter may be an early event in the process of tumorigenesis^[26]. Additionally, it is also important to point out that more frequent hypermethylation of CFTR promoter was observed in prostate cancer patients with a high Gleason score and Ki-67 index^[24], indicating that CFTR hypermethylation could be used to predict prognosis in prostate cancer. Based on the study of CFTR hypermethylation in lung cancer, it is possible that CFTR may function as a tumor suppressor in these cancers as well, which is partly supported by the findings in prostate cancer^[28] that the CFTR knockdown promoted cancer cell proliferation, invasion and migration.

The role of CFTR in breast cancer has been investigated since the 1990s, but the findings are controversial. According to the cohort study conducted by Neglia *et al.*^[32] breast cancer is less common in CF patients. In 1996, Abraham *et al.*^[60] reported that the CF phenotype with elevated blood ATP concentration yielded decreased tumor growth and implantation in mice. The authors believed that dysfunctional CFTR in the digestive duct failed to excrete ATP into gut lumen resulting in elevated blood ATP, which is cancer suppressive. However, recently Zhang *et al.*^[29] reported that the down-regulation of CFTR promoted cell migration and invasion *in vitro* as well as metastasis *in vivo* while over-expressing CFTR reversed these activities. Although this seems controversial, the findings indicate that the role of CFTR in cancer depends, at least partially, on the pathological conditions of the individuals. Under the CF condition, in which the CFTR and other CFTR-regulated ion channels/transporters are dysfunctional, the de-regulated transport activity due to dysfunctional CFTR may

be the main factor that contributes to the pathogenesis of cancer. When the CFTR is functional, it is possible ion transportation activities do not account for the main aspect of the tumorigenesis.

CFTR has also recently been related to cervical cancer^[61-63]. A series of studies from Peng *et al*^[61] demonstrated that the expression of CFTR is gradually increased from normal to pre-cancerous cervical tissue and cervical cancer tissues, and it is also positively correlated to histological grades, tumor stage, and metastatic grades. In addition, further investigation by the Peng *et al*^[61] indicated that the upregulated CFTR in pre-cancerous and cervical cancer tissues resulted from aberrantly increased NF- κ B p65 translocation^[62]. RNA sequencing results obtained from samples co-existing with pre-cancerous lesions and adjacent normal cervical tissue demonstrated that CFTR was also significantly up-regulated in cervical cancer^[63], which is in agreement with the findings from Peng *et al*^[61] and Wu *et al*^[62]. These findings are opposite of those from other types of cancers which demonstrated the tumor suppressive roles of CFTR, indicating that the role of CFTR in cancer is organ/system specific. Although CFTR has been originally identified as a chloride channel, accumulating evidence has demonstrated it has different functions in different models, suggesting that the function of CFTR is organ/system dependent, and consequently the role of CFTR in different cancers may also be organ/system specific.

MOLECULAR MECHANISMS LINKING DYSFUNCTIONAL CFTR AND CANCERS

Investigations have been performed to propose molecular mechanisms to link defect found in CFTR to cancer, the underlying mechanism of which can be divided into two major subgroups depending on the different aspects of the CFTR function.

One subgroup is based on the transporter feature of CFTR. As a transporter located on the epithelial membrane, CFTR is able to transport ATP across the membrane^[64]. On the other hand, it is demonstrated that extracellular ATP processes an inhibitory effect on tumor growth both *in vitro* and *in vivo*^[65,66]. In gastrointestinal cancers, CFTR dysfunction or dysregulation leads to decreased luminal ATP, which may account for the elevated cancer incidence. However, as a result of decreased ATP secretion into gut lumen, the blood concentration of ATP increased, probably resulting in decreased malignancy such as breast cancer^[60]. This explains, to some degree, why CFTR dysfunction promotes the risk of certain types of cancer while suppresses the risk in others. In addition, the transporting property of CFTR is also linked to the apoptosis and survival of cells. CFTR is reported to be able to transport glutathione (GSH), an important antioxidant protecting cells from excessive oxidative stress, out of cells during apoptosis^[67]. This activity is hampered when CFTR is dysfunctional or the expression of CFTR is too low, which are common in several types of cancers. In addition, metabolites such

as CO₂ and lactate are generated by fast tumor growth, resulting in an acidic and hypoxic microenvironment around cancer cells. Functional CFTR facilitates the survival of cancer cells *via* transporting bicarbonate out of the cells^[68]. Therefore, CFTR seems to possess both cancer promoting and suppressing properties, but the exact role it plays in a particular cancer may depend on the cancer type and tumor microenvironment.

The other subgroup, which is more complicated and independent of the transporter feature of CFTR, is based on the signaling and protein-protein interactions that CFTR is involved in. It is well established that NF- κ B pathway, an important player in cancer proliferation and cell survival^[69,70], is negatively regulated by functional CFTR^[57,71]. Meanwhile, decreased NF- κ B activity was also observed in CFTR over-expressed lung cancer cells^[72]. Recently, CFTR was found to be associated with tumor metastasis in multiple cancers in which uPA/uPAR pathway is involved^[28,54]. Although the mechanisms are not fully understood, these investigations have shed light on the importance of the NF- κ B related signaling. Moreover, Ras, PKC, IL-1 β , and IFN- γ are involved in the down-regulation of CFTR in cancer cells^[43-45,73]. In addition, CFTR has been shown to physically interact with other proteins such as ZO-1, afadin, and E-cadherin contributing to various cellular activities^[48,55,56], and the disruption of these interactions leads to enhanced cell invasion and migration, indicating that CFTR plays more complicated roles than previously thought. Further, CFTR promoter hypermethylation is also observed in multiple types of cancer including hepatocellular cancer, lung cancer, bladder cancer, and prostate cancer^[22,24-26,58]. It is still not clear whether this epigenetic modification occurs at early stages or is a result of tumorigenesis, although a study in hepatocellular cancer suggests that the methylation may be an early event of cancer progression^[26]. Conclusively, CFTR functions not only as an ion channel/transporter but also as a signaling hub involved in multiple signaling pathways and macromolecular complexes, contributing to seemingly opposite cellular functions: Either promoting or suppressing cancer progression.

CONCLUSION

CFTR, a glycoprotein with 1480 amino acids, was originally identified as a chloride channel that transports chloride ions in and out of cells. Emerging evidence suggests that CFTR possesses both tumor promoting and tumor suppressing properties as shown in Table 1. However, the exact role it plays in cancer depends on the cancer type and the microenvironment of the cancer cells. Since the expression of CFTR differs from one organ to another, it is possible that the functions of CFTR in different organs are also different. For instance, in the pancreas CFTR is mainly responsible for excretion^[74] while in macrophages it contributes to controlling cytokine production^[75]. In addition, the microenvironment of cancer cells also dictates the role of CFTR. There is variation in proteins expressed in different cancer cells as well as cytokines

Table 1 Summary of impact of cystic fibrosis transmembrane regulator on the malignancies of different organs

Organs	Impact	Ref.
Pancreas	Wildtype CFTR suppresses tumor progression	[23,32-34,38,39]
Colon	CFTR dysfunction my results in obstruction of pancreatic duct and chronic inflammation CFTR dysfunction increases the risk of colon cancer	[40-46,48,73]
Stomach	Wildtype CFTR may act as a tumor suppressor in colon cancer	
Lung	Serum CFTR is associated with gastric cancer staging CFTR mutation is associated with increased risk of lung cancer	[49] [22,32,50,51,54]
Prostate	CFTR expression is also associated with tumor progression and poor prognosis	
Liver	CFTR gene was hypermethylated in prostate cancer cells	[24,58]
Bladder	CFTR gene was hypermethylated in hepatocellular cancer cells	[26,59]
Breast	CFTR gene was hypermethylated in bladder cancer cells	[25]
Cervix	Suppresses breast cancer by elevating blood ATP but promotes cancer metastasis by enhancing EMT Promotes cancer progression	[29,32,60] [61-63]

CFTR: Cystic fibrosis transmembrane regulator; EMT: Epithelial-mesenchymal transition.

or chemokines produced in different types of cancers, generating different microenvironment around the cells. Consequently, CFTR may react differently according to environmental stimulants. For example, IFN- γ and TNF- α down-regulate the expression of CFTR, while cAMP up-regulates the expression of CFTR in cancer cells^[76,77]. Even though the biology of CFTR has been investigated for decades, its function is still not fully understood, especially in cancer cells. Based on the literature to date, it will be helpful to study the protein interactome and the signaling pathways associated with CFTR in cancer cells. In addition, previous studies of CFTR dysfunction were largely based on CF related CFTR gene variations, and most of the studies usually only covered very small amounts of mutations, though over 1900 CFTR mutations have been documented so far. This may limit the findings and/or conclusions from these studies. In order to obtain a more comprehensive knowledge of CFTR biology and its role in cancer, interdisciplinary collaborations using system biology and integrative approaches are encouraged.

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