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REVIEW

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Cystic fibrosis transmembrane conductance regulator (CFTR): beyond cystic fibrosis

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Abstract

Background: The cystic fibrosis transmembrane conductance regulator (*CFTR*) gene has been traditionally linked to cystic fibrosis (CF) inheritance in an autosomal recessive manner. Advances in molecular biology and genetics have expanded our understanding of the *CFTR* gene and its encoding products expressed in different tissues.

Aim: The study's aim consists of reviewing the different pathological CF phenotypes using the existing literature. We know that alterations of the CFTR protein's structure may result in different pathological phenotypes.

Methods: Open sources such as PubMed and Science Direct databases have been used for this review. We focused our selection on articles published within the last 15 years. Critical terms related to the CFTR protein have been used: "CFTR AND cancer," "CFTR AND celiac disease," "CFTR AND pancreatitis," "children," "adults," "genotype," "phenotype," "correlation," "mutation," "CFTR," "diseases," "disorders," and "no cystic fibrosis."

Results: We analyzed 1,115 abstracts in total. Moreover, only 189 were suitable for the topic. We focused on the role of CFTR in cancer, gastrointestinal disorders, respiratory diseases, reproductive system, and systemic hypertension.

Conclusions: Mutations in *CFTR* gene are often associated with CF. In this review, we highlighted the broad spectrum of alterations reported for this gene, which may be involved in the pathogenesis of other diseases. The importance of these new insights in the role of CFTR relies on the possibility of considering this protein/gene as a novel therapeutic target for CF- and CFTR-related diseases.

Keywords: CFTR, Cancer, Gastrointestinal disorders, Celiac disease, Autoimmune disease, COPD

Introduction

The gene that encodes the human cystic fibrosis transmembrane conductance regulator (*CFTR*) protein is located on the long arm of chromosome 7. It encodes for a membrane protein, specifically the ATP-binding cassette transporter-class ion channel protein that conducts chloride and thiocyanate ions across epithelial cell membranes. Mutations in the *CFTR* gene result in cystic fibrosis (CF), an autosomal recessive disorder. Since its discovery in 1989, over 2,300 variations are reported for the *CFTR* gene [1, 2].

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Genetic testing availability and accessibility have broadened the spectrum of genotypes related to *CFTR* and the genotype–phenotype correlation, especially for milder phenotypes [3–5]. CFTR is expressed in different tissues and organs, mainly lung, gastrointestinal, and reproductive systems. Mutations affecting chloride ion channel function might lead to dysregulation of epithelial fluid transport in the lung and pancreas and affect other organs [6, 7].

New evidence has, recently, reconsidered the role of *CFTR* in diseases other than cystic fibrosis [8]. CFTR dysfunctions have been reported in high-heavy diseases such as cancer, celiac disease, and chronic obstructive pulmonary disease (COPD) [8]. Unlike CF, the suggested underlying pathogenic mechanisms include heterozygous

mutations and an acquired dysfunction, such as epigenetic mechanisms [8]. This study reviews the existing literature on the different pathological phenotypes other than CF caused by alterations to the CFTR protein.

Methods

Research strategy

Open sources such as PubMed and Science Direct databases have been used for this review. We focused our selection on articles published within the last 15 years. Critical terms related to the CFTR protein have been used: "CFTR AND cancer," "CFTR AND celiac disease," "CFTR AND pancreatitis," "children," "adults," "genotype," "phenotype," "correlation," "mutation," "CFTR," "diseases," "disorders," and "no cystic fibrosis."

Study selection

The following inclusion criteria have been considered in the article selection: English language, publication in peer-reviewed journals, published since 2006. All the articles irrelevant to the investigated issue have been excluded by title, abstract, or full text. Articles concerning cystic fibrosis were excluded. The studies containing inclusion criteria in the abstract have been considered for clarification. The selection has been extended to article's references with similar inclusion criteria. A final number of 189 of 1,115 abstracts have satisfied the inclusion criteria.

CFTR and cancer

A growing number of studies have recently highlighted a correlation between mutations in the *CFTR* gene and different types of cancers [9–36, Table 1]. The role of CFTR in cancer seems to be variable according to the neoplasm, probably due to the influence and interaction with different tissue microenvironments [9].

A large population-based study on around 500,000 individuals assessed the association between CFTR mutation carriers, specifically F508del, and the risk of 54 types of cancers using the United Kingdom Biobank data [10]. Compared to non-cancer subjects, a significantly higher *CFTR* F508del mutation rate was found in individuals affected by colorectal ((OR 1.17 (95% CI 1.02–1.32, $p=0.02$)), gallbladder and biliary tract ((OR 1.92 (95% CI 1.20–2.91, $p=0.004$)), thyroid cancer ((OR 1.47 (95% CI 0.99–2.08, $p=0.04$)), and non-Hodgkin's lymphoma ((OR 1.32 (95% CI 1.04–1.65, $p=0.02$)) [10], and remained significantly high after multivariable analysis. Overall, lung cancer risk was reduced; however, in a similar study on Danish *CFTR* F508del, an increased risk of lung cancer was observed ((OR 1.52 (95% CI 1.12–2.08, $p=0.008$)) [11]. No significant association between mutations and pancreatic cancer ((OR 1.2 (95% CI 0.85–1.64)) was observed [10]. This was consistent with Schubert et al. about pancreatic cancer, though they had a smaller study of 31 different *CFTR* mutations [12]. Nevertheless, a meta-analysis identified a modest but significantly increased risk of pancreatic cancer in four of the 13 *CFTR* mutation carriers (OR 1.41, 95% CI 1.07–1.84, $p=0.013$, [mutations: F508del, W1282X, ΔI507, S549R]) [13]. Thus, this difference might be attributable to the spectrum of mutations analyzed.

The role of *CFTR* in cancer pathogenesis is not limited to gene mutations, but also through epigenetic modifications [14]. It has been suggested that the expression of *CFTR* was downregulated in patients affected by esophageal cancer ($p<0.05$). Indeed, CFTR overexpression inhibited the growth and migration of esophageal cancer cells by downregulating protein expression of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) ($p<0.05$). Conversely, *CFTR* silencing led to an increase in NF-κB-p65 and -p50 expression and increased tumor invasion, and growth in mice. [15].

Similarly, in colorectal cancer, CFTR expression was downregulated compared to normal tissues ($p=0.034$), possibly due to the *CFTR* promoter's methylation. Interestingly, *CFTR* overexpression acts as a tumor suppressor and reduces cell migration and invasion [16], possibly through increased Wnt/beta-catenin signaling evidenced in CFTR knock-out mice, though this data remains to be verified [17]. Liu et al. found that knocked down CFTR colorectal cancer cells reduced heat shock protein 90 (HSP-90) expression ($p<0.01$), leading to altered AKT and extracellular-regulated kinase (ERK) signaling pathways. Reduced AKT ERK signaling pathways determined mitochondrial dysfunction by inhibiting the Bcl-2 family proteins involved in apoptosis [18].

Hypermethylation of the *CFTR* promoter is observed in head and neck cancer and non-small cell lung, bladder, hepatic/hepatocellular, and breast cancer [19–23]. In the latter, *CFTR* silencing may lead to loss of E-cadherin, which assists in cell adhesion. The loss of E-cadherin correlates with invasion and metastasis [20, 24].

CFTR is expressed in the epithelial cells along the female reproductive tract [25]. *CFTR* overexpression in ovarian cancer is positively associated with severe cancers, at an advanced stage, and have a higher degree of malignancy, based on 112 tissue samples (83 epithelial ovarian cancer) ($p<0.05$). The authors suggested a possible interaction with intracellular c-Src signaling pathways involved in cellular growth [26]. A similar observation concerning *CFTR* overexpression was reported in cervical cancer ($p<0.01$), where it was associated with poorer prognosis, stage and metastasis. [27]. However, a more recent study contradicted these results, reporting that *CFTR* overexpression mediated the inhibition of the

Table 1 Summary of main studies about *CFTR* and cancer

Authors	Setting	Sample size	Major findings
Shi et al. [19]	Population-based study	498.930 individuals aged 40–69 years	F508del carriers: ↑risk for colorectal, gallbladder and biliary tract, thyroid cancer, non-Hodgkin's lymphoma ↓ risk for lung cancer no risk for pancreatic cancer
Colak et al. [11]	Population-based study median follow-up of 9 years	108.034 individuals	F508del carriers: ↑ risk for lung cancer ↑ chronic bronchitis ↑ bronchiectasis,
Schubert et al. [12]	Case control study	121 pancreatic cancer 102 idiopathic chronic pancreatitis 130 controls	*CFTR* mutation carriers (34 different mutations): no risk for pancreatic cancer
Cazacu et al. [13]	Meta-analysis 5 studies	1674 pancreatic cancer 19.036 controls	F508del, W1282X, ΔI507 and S549R carriers: ↑ risk for pancreatic cancer
Li et al. [15, 34]	Case series	40 individuals with esophageal cancer	CFTR downregulation ↑ NF-κB-p65 ↑ NF-κB-p50
Liu C et al. [16]	Case series Case control study	35 colorectal and adjacent tissue samples	*CFTR* downregulation *CFTR* overexpression suppress tumor proliferation
Liu K et al. [18]		Colorectal cancer cells	*CFTR* knockdown cells induces mitochondrial dysfunction through: ↓ HSP90 ↓ AKT, ERK ↓ Bcl-2
Liu K et al. [20]		19 breast cancer and normal tissue samples	*CFTR* promoter hypermethylation associated with invasion and worse prognosis
Xu et al. [26]		83 epithelial ovarian cancer samples	*CFTR* is overexpressed in ovarian cancer
Peng et al. [27]		357 cervical tissue samples Cervical cell lines	*CFTR* is overexpressed in cervical cancer and correlates with prognosis, stage and metastasis
Wu et al. [28]	Case control study	135 cervical tissue samples	*CFTR* overexpression correlates with ↓cell proliferation, migration, and invasion ↓ NF-κB Signaling Pathway
Xia et al. [29]	Case control study	40 endometrial carcinoma samples and 40 controls	*CFTR* overexpression But *CFTR* inhibition associated with increased cell proliferation through ↓ (miR)-125b
Xie et al. [30]	In vivo In vitro	Prostate cancer samples and cell lines	*CFTR* is downregulated *CFTR* tumor suppressor through miR-193b inhibition on uPA
Tu et al. [31]	Case control study	225 nasopharyngeal carcinoma tissue samples	*CFTR* is downregulated and correlate with advanced stage, poor prognosis and metastasis
Zhong et al. [32]	In vitro	153 human glioblastoma cell lines	Lower CFTR correlate with poor prognosis CFTR potentiators reduces cell proliferation through JAK2/STAT3 inhibition
Li et al. [15, 34]	In vitro	Adenocarcinoma lung cancer cell lines A549	*CFTR* overexpression acts as a tumor suppressor
Yang et al. [35]	Case control study In vitro	138 patients with acute Leukemia 50 normal human samples	*CFTR* overexpression in acute lymphoblastic leukemia CFTR inhibits PP2A phosphatase antitumoral activity *CFTR* inhibitors reduces tumor growth

NF-κB p65 signaling pathway and reduced cell proliferation and tumor invasion [28]. In endometrial carcinoma, increased CFTR mRNA expression was identified ($p < 0.05$). Nevertheless, inhibition of *CFTR* with the *CFTR* inhibitor 172 promoted cell proliferation through reduced micro-RNA (miR)-125b, which acts as a tumor suppressor, decreasing the expression of matrix metalloproteinase 11 (*MMP11*), and vascular endothelial growth factor (VEGF) −A ($p < 0.05$) [29]. Further, high levels of urokinase plasminogen activator (uPA) are observed in prostate cancer, which leads to cell proliferation. Interestingly, a high association between *CFTR* expression and

miR-193b expression was identified in those with prostate cancer. A reduction in *CFTR* expression leads to a reduction in miR-193A, with subsequent lack of inhibition of its target, the uPA [30]. Thus, these findings provide evidence for the many different interactions between *CFTR* and different signaling pathways, which goes beyond the original role of CFTR as an ion channel only.

The importance of detailed genetic characterization in cancer might have implications for diagnosis, prognosis, and treatment. Tu et al. identified *CFTR* downregulation in 225 cases of nasopharyngeal cancer. After multivariate analysis, *CFTR* downregulation resulted as an independent prognostic factor ($p=0.003$), correlating with advanced cancer stages ($p=0.026$), increased metastasis ($p<0.001$), and poor prognosis ($p<0.01$) [31]. Although lower *CFTR* expression was associated with a poor prognosis in 153 patients with glioblastoma ($p=0.04$) [32], increased *CFTR* expression was also not beneficial to prostate cancer prognosis because it correlated with chemotherapy resistance [33]. However, Xie et al. reported that CFTR overexpression, whose was downregulated in prostate cancer by hypermethylation, suppressed prostate cancer progression in vitro and in vivo [30]. The emerging role of *CFTR* in cancer represents an intriguing potential therapeutic target. Indeed, like Forskolin and Cact-A1, *CFTR* activators demonstrated an antiproliferative effect on glioblastoma by significantly reducing Ki67 positive cells ($p<0.05$) [32]. *CFTR* activation may decrease phosphorylation of Janus kinase 2/signal transducer and activator of transcription-3 (JAK2/STAT3) signaling pathway. This effect was attenuated by *CFTR*-inh172 ($p<0.05$) [32, 33]. *CFTR* overexpression exerted a similar influence on lung adenocarcinoma Ki67 positive cells, as well as on cells' invasion and migration. *CFTR* overexpression was also effective to inhibit clonogencity induced by nicotine exposure ($p<0.01$) [34].

In contrast to this, in diseases where the Philadelphia chromosome is present, leading to T-cell acute lymphoblastic leukemia, *CFTR* expression was higher than normal controls ($p<0.001$), Philadelphia chromosome negative acute lymphoblastic leukemia and chronic myeloid leukemia cells) ($p<0.01$). Further, using the *CFTR* inhibitor, *CFTR*-inh172, inhibited T-cell acute lymphoblastic leukemia growth. The underlying mechanism of cell proliferation in this subtype of leukemia involved activating the p-BCR-ABL and Wnt/β-catenin signaling pathway. This leads to constant CFTR activation, which mediated inhibition of protein phosphatase 2A (PP2A) antitumoral activity [35, 36].

In summary, studies on cancer have overcome the conception of CFTR as a mere ion channel and transporter but showing pleiotropic interactions with proteins from different intracellular signaling pathways. The disruption of these pathways is from the consequence of gene mutations and the result of epigenetic modifications.

CFTR and gastrointestinal disorders

The most common gastrointestinal disorder associated with *CFTR* mutations is pancreatic insufficiency and pancreatitis in the setting of CF [37]. However, a fourfold increased risk of *CFTR* mutation carriers in idiopathic chronic pancreatitis (ICP) sufferers also has emerged, though the small sample size (OR 4.3, 95% CI 2.1–8.7, $p=0.0002$). Further, Cohn extended the analysis to three previous studies. Overall, 14 *CFTR* mutation carriers out of 155 individuals with ICP were found, and the OR was 2.9 (1.7–4.9, $p<0.0001$) [38]. The p.R75Q *CFTR* heterozygous variant is associated with ICP (OR = 3.43, 95% CI 1.7–6.8). The risk for ICP was much higher with the serine peptidase inhibitor (*SPINK*) 1 heterozygous variant (OR = 62.5, 95% CI 16.6–95.4). Other *CFTR* variants, except for F508del, became significant only when inherited together with *SPINK1* variants, which may be due to CFTR impaired HCO_3^- conductance and not chloride conductance in p.R75Q carriers. Overall, *CFTR* carriers, including CF-causing variants, had an OR of 7.4 (95% CI 2.3–18.5) of those with ICP [39]. Two previous review study partially reconsidered these results, highlighting the predominant role of *SPINK1* in those with ICP when non-CF-causing variants, such as p.R75Q, were detected. Their rate was not significantly different compared to controls carrying SPINK1 variants [40, 41].

Beyond *CFTR*, the most common genes associated with ICP were the cationic trypsinogen gene (*PRSS1*), *SPINK1*, and *CTRC* gene. In a Chinese cohort of 715 individuals with ICP, isolated *CFTR* variants were not significantly associated with ICP compared with 1,196 controls ($p>0.05$) [42]. Therefore, although the association between *CFTR* and pancreatitis has been widely investigated, there are still contradictory results due to the complex genetic background and interactions between environmental factors.

Other gastrointestinal disorders should be added within the spectrum of the *CFTR* gene mutations and dysfunctions. These include secretory diarrheas, altered bile acid homeostasis, primary sclerosing cholangitis, and celiac disease [43]. CFTR targets bacterial enterotoxins on the intestinal epithelial cell membrane, which induce cAMP- or cGMP-mediated protracted activation of *CFTR*, leading to subsequent water loss and dehydration, typical features of secretory diarrheas. Thus, *CFTR* inhibitors, like *CFTR*-inh172, could represent a potential target therapy in secretory diarrheas. However, some limitations include the difficult localization of CFTR in the intestinal crypts and other ion channels' involvement in the pathogenesis of secretory diarrheas [43, 44].

Another organ affected by CFTR dysfunction is the gallbladder, as evidenced in CFTR knock-out mice, which showed impaired gallbladder emptying ($p < 0.05$), probably due to vasoactive intestinal peptide (VIP) overexpression which acts as a myorelaxant on gallbladder, and bile acid homeostasis [44]. Primary sclerosing cholangitis (PSC) is a chronic cholestasis condition associated with biliary inflammation, obliteration, and fibrosis [45]. Though PSC pathogenesis has been associated with specific HLAs (HLA-DRB1*1501-DQB1*0602, HLA-DRB1*1301-DQB1*0603, and HLA-A1-B8-DRB1*0301-DQB1*0201) and often with inflammatory bowel disease, a role for *CFTR* in PSC development has been suggested [46, 47]. Sheth et al. reported a significant increase in heterozygous *CFTR* variants in seven out of 19 (37%, 95% CI: 16–62%) individuals affected by PSC compared to inflammatory bowel disease and primary biliary cirrhosis patients ($p < 0.02$) [47]. In a cohort of 32 patients with PSC who underwent next-generation sequencing, six had *CFTR* disease causing mutations on one allele (OR = 6.1–95% CI 2.2–16.7, $p = 0.002$), and 19 carried at least one *CFTR* polymorphism. However, six had abnormal, and 21 had intermediate sweat tests associated with CF-like phenotype [48]. Previous studies questioned the relationship between CFTR and PSC, which did not find significant differences between patients with or without PSC and the prevalence of CFTR mutations. Nevertheless, these studies may be biased by the limited number of modifications analyzed [48, 49].

Celiac disease (CD) is strictly associated with HLA DQ2/DQ8 predisposition [50]. The evidence that CF patients reported having a significantly higher CD incidence ($p = 0.0007$) has led to an investigation of CFTR's function in patients with CD [51, 52]. Interestingly, Villella et al. revealed new insights in such a disease's pathogenesis, suggesting a *CFTR* role as a gluten target [53]. In previous studies, CFTR has been identified as a regulator of proteostasis, an essential cytoprotective mechanism to remove misfolded or polyubiquitylated proteins. Its dysfunction was associated with lung inflammation due to autophagy inhibition, mediated by tissue transglutaminase 2 (TGM2), a key enzyme involved in CD [54]. Villella et al. showed that alpha-gliadin-derived LGQQQPFPPQQPY peptide (P31–43) inhibits the ATPase function of CFTR by binding with the nucleotide-binding domain-1 (NBD1) of CFTR on intestinal epithelial cells of mice with CD-predisposing HLA. NBD1 interaction with P31–43 happened only when it is in a closed conformation. This has consequences on downstream pathways, the tissue transglutaminase 2 (TGM2), and the autophagy protein Beclin-1 (BECN1). Indeed, TGM2 activation, in response to CFTR inactivation, led to reduced BECN1 with impaired proteostasis, determining a pro-inflammatory state. Therefore, TGM2, inhibiting NF-κB inhibitor alpha (NFKBIA), determined increased NFκB and inflammasome activation with IL-15 and IL-β production, respectively. These initiate an immune response against gliadin [53].

The previously mentioned interactions created a vicious cycle that amplifies and further worsen *CFTR* inhibition. Hence, Maiuri et al. introduced the definition of "infernal trio" regarding CFTR inhibition, TGM2 activation, and autophagy impairment. For example, TGM2 activation promoted CFTR crosslinking with P31-43, creating a trimolecular complex, which made *CFTR* inhibition irreversible [55]. In the light of this mechanism, and the affinity of P31-43 peptide to the closed conformation of CFTR, potentiators of CFTR may be a therapeutic option in celiac disease, by promoting CFTR channel opening. VX-770 (Ivacaftor), a CFTR potentiator, seemed to effectively reduce gliadin-induced inflammation in vitro, especially IL-15 production and NF-kB p65, making CFTR a potential new therapeutic target in CD. Furthermore, VX-770 also prevented gliadin mediated inhibition of CFTR and promoted a tolerogenic response in gluten-sensitive mice and cells from celiac patients [53].

Genistein, a phytoestrogen contained in soy, targets CFTR and acts as a channel gating potentiate. In the context of celiac disease, it was able to prevent P31-43 induced epithelial stress and inflammation, both in vitro and in vivo animal models [56].

Drugs targeting CFTR may find application in two other autoimmune diseases, idiopathic autoimmune pancreatitis and Sjogren's syndrome, characterized by disrupted fluid secretion in pancreatic ducts and of saliva and lacrimal glands, respectively. Indeed, in Sjogren's syndrome mice model *CFTR* expression was reduced and treatment with VX-770 and C18 increased salivation, ductal fluid secretion, and reduced inflammation. Similar results were obtained in a pancreatic inflammation model. Furthermore, C18 restored CFTR expression in the ducts of salivary glands. Interestingly, this had also effects on acinar cells, where Aquaporin 5 expression was recovered [57]. Table 2 summarizes the main studies about *CFTR* and gastrointestinal disorders.

CFTR and the lungs

Recently, acquired CFTR dysfunctions was found to occur in highly prevalent diseases such as chronic obstructive pulmonary disease (COPD) with a chronic bronchitis phenotype [58]. Indeed, cigarette smoke exposure reduces CFTR expression and activity, both in vitro and in vivo, contributing to mucociliary clearance impairment. Interestingly, CFTR dysfunction was not limited to the lungs but was evidenced in other areas, suggesting

Table 2 Summary of main studies about *CFTR* and gastrointestinal disorders

Authors	Setting	Sample size	Major findings
Cohn et al. [38]	Meta-analysis	152 individuals with ICP	CF carriers who have one CF-causing mutation plus one normal allele have 2.9 times higher risk for ICP
Schneider et al. [39]	Case control study	80 ICP patients 95 controls	*CFTR* p.R75Q carriers 3.4 times higher risk for ICP p.R75Q + SPINK1 mutation 62.5 times higher risk for ICP
Zou et al. [42]	Case control study	715 ICP patients 1196 controls	Isolated *CFTR* mutations non-significant increased risk for ICP
Sheth et al. [47]	Case control study	19 PSC patients 35 disease controls	Higher rate of *CFTR* variants in PSC
Werlin et al. [48]	Case series	32 PSC patients	19 had at least one *CFTR* polymorphism 6 had a *CFTR* causing mutation on one allele
Villella et al. [53]		CD-predisposing HLA mice model Human intestinal epithelial cells sensitive to gliadin	P31–43 derived gliadin peptide inhibits *CFTR* leading to transglutaminase activation and inflammatory state CFTR potentiator reduces gliadin-induced inflammation
Zeng et al. [57]		Non obese diabetic mice model of AIP or Sjogren's syndrome Pancreatic and parotid tissue samples	Reduced CFTR expression CFTR potentiators restore ductal CFTR and this restore acini, gland functions and fluid secretions

a potential role in the onset of smoke-related complications such as Mellitus diabetes, male infertility, and idiopathic pancreatitis [59]. The hypothesized mechanism may be attributable to acrolein, which induces structural changes to the CFTR channel, or cadmium and arsenic [59–61]. As regards cadmium, it showed to reduce *CFTR* expression ($p < 0.001$), both in vitro and in vivo, in a dose- and time-dependent manner and CFTR channel activity [60]. A similar effect was described for arsenic through ubiqutin-mediated lysosomal degradation of CFTR and reduced chloride secretion in vitro ($p < 0.05$) [61]. In a double-blind, placebo-controlled study on 92 COPD patients, the CFTR potentiator Icenticaftor 300 mg effectively improved FEV1 after 28 days (mean 50 mL for pre-bronchodilator FEV1 and mean 63 mL for post-bronchodilator FEV1), while no significant improvement was seen in the lung clearance index [62].

In a population-based study, 2858 carriers of *CFTR* F508del were identified and had an increased risk of chronic bronchitis (HR 1.31, 95% CI 1.16–1.48), bronchiectasis (HR 1.88, 95% CI 1.03–3.45), and lung cancer (HR 1.52, 95% CI 1.12–2.08). However, this study's main limitation is the lack of investigations for mutations different from F508del, which may be responsible for compound heterozygosis [11].

Bronchial asthma is certainly one of the main chronic diseases of the respiratory system [63, 64]. Although the risk of asthma was not higher than the general population, a meta-analysis of 15 studies (2.113 asthma cases and 13.457 controls) on *CFTR* mutations carriers, which contained 34 different pathogenetic variants, reported an increased risk of asthma (OR 1.61, 95% CI 1.18–2.21) [65]. Table 3 summarizes the main studies about *CFTR* and lung disorders.

CFTR and the reproductive system

Congenital bilateral absence of the vas deferens (CBAVD) accounts for approximately 3% of infertility cases. Because almost all infertile CF males exhibit CBAVD, it is widely considered an atypical form of CF and a CFTR-related disorder [7]. Interestingly, a meta-analysis on 38 studies found that 28% (95% CI 24–32%) of individuals

Table 3 Summary of main studies about *CFTR* and lung diseases

Authors	Setting	Sample size	Major findings
Raju et al	Review		Cigarette smoke induces *acquired* CFTR dysfunction with impaired mucociliary clearance through acrolein, cadmium and arsenic COPD patients shows reduced CFTR with also pathological systemic consequences
Nielsen et al. [65]	Meta-analysis	15 studies 2.113 asthma cases 13.457 controls	Heterozygous CF carriers have higher risk for asthma (OR 1.61, 1.18–2.21)

Table 4 Summary of main studies about *CFTR* and reproductive system

Authors	Setting	Sample size	Major findings
Yu et al. [66]	Meta-analysis	38 studies 2744 individuals	28% of men with CBAVD had only one *CFTR* mutation
Chen et al. [69]	Ovarian follicles from rat PCOS model and control		*CFTR* is downregulated in PCOS and affects/impairs FSH-mediated granulosa cell proliferation in follicles
Zhang et al. [70]	Mice CFTR knock-out model		Possible role of *CFTR* in regulating blood pressure

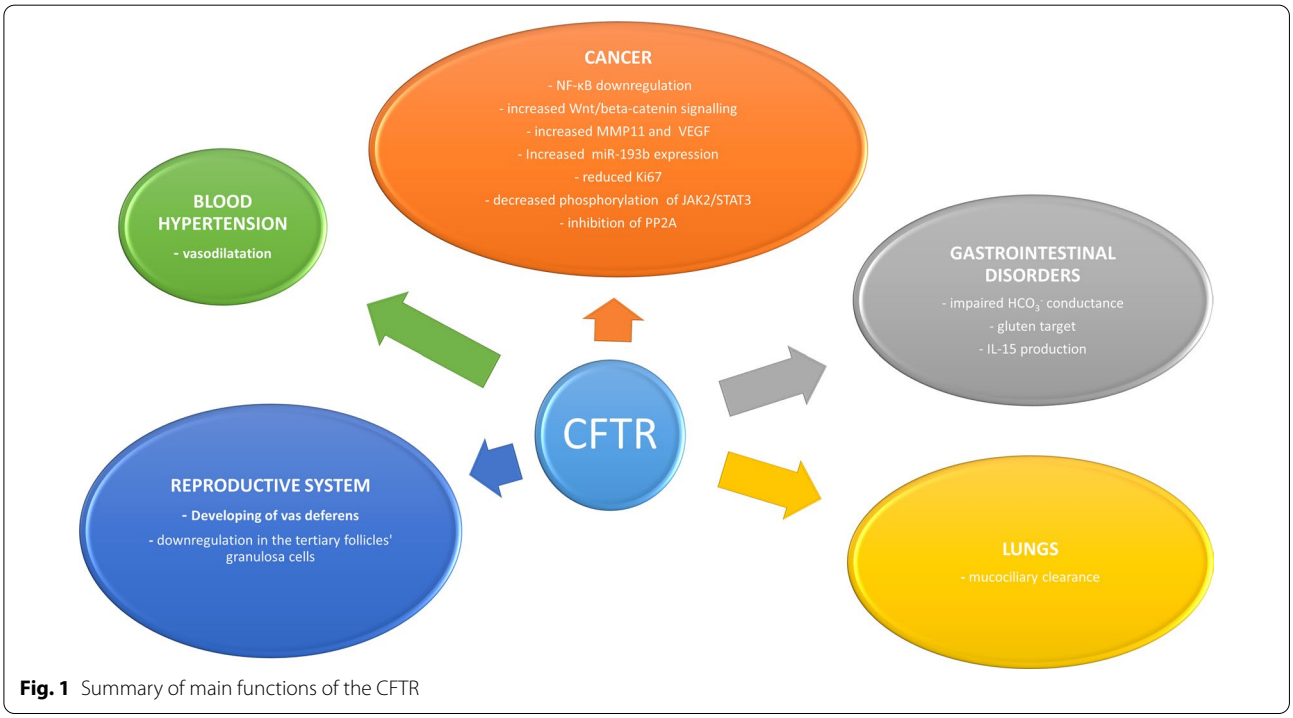

Fig. 1 Summary of main functions of the CFTR

with CBAVD carried only one *CFTR* mutation. However, there is a considerable risk of bias because of the included study's heterogeneity (Egger's test $p=0.874$), which might not have investigated less common *CFTR* [66]. Recently, heterozygous copy number variants of *CFTR* have also been suggested to play a role in the pathogenesis of CBAVD, reported to affect five (1.9%) of 263 Chinese affected individuals. Among these, four out of five carried a *CFTR* partial deletion [67].

Regarding the female reproductive system, in polycystic ovarian syndrome (PCOS), CFTR and aromatase expression was downregulated in granulosa cells, both in rat model and human, compared with non-PCOS women ($p<0.05$). Hence, Chen et al. found that *CFTR* enhanced follicle-stimulating hormone (FSH) mediated aromatase expression through HCO_3-induced cAMP response element-binding protein (CREB) phosphorylation [68]. In a more recent study, the CFTR/HCO_3-/sAC signaling pattern was further elucidated, contributing to MAPK/ERK downstream pathways of cell proliferation. Therefore, defective CFTR decreased granulosa cell proliferation and contributed to altered follicle formation, typical of PCOS [69]. Table 4 summarizes the main studies about *CFTR* and reproductive system disorders.

CFTR and cardiovascular system

CFTR seems to be involved in blood pressure regulation. *CFTR* knock-out mice developed higher mean blood pressure compared with controls ($p<0.05$). This evidence was supported by *CFTR* downregulation in a model of induced hypertension, where a high fructose and salt diet reduced With-No-Lysine K (WNK) kinase expression in arteries and subsequently *CFTR* expression, leading to increased vascular constriction. This was further supported by the evidence that *CFTR* knock-out mice fed with high fructose and salt dose did not show increased mean blood pressure ($p<0.05$). [70]. However, further studies are needed to confirm these preliminary data.

Conclusions

Mutations in *CFTR* gene are often associated with CF. In this review, we highlighted the broad spectrum of alterations reported for this gene, which may be involved in the pathogenesis of other diseases [Fig. 1]. The extensive application of genetic testing provides evidence to link the *CFTR* gene mutation with different conditions and characterize their genotype-phenotypes. The importance of these new insights in the role of *CFTR* relies on the possibility of making it a novel therapeutic target. In this context, results obtained by the new CFTR modulators in CF are promising, highlighting their ability to modify the disease course. Therefore, they might improve treatment of high burden diseases through precision medicine [71]. However, despite the ubiquitous role of CFTR is various organ systems, there is still a dearth of CFTR-based therapeutics. Some of the reasons might be unstable pharmacokinetics, cross-talk with other cellular proteins, and sampling issues for clinical trials. These points have to be considered while developing CFTR-based therapeutic interventions.

Abbreviations

AKT: Protein kinase B; ATP: Adenosine triphosphate; BECN1: Beclin-1; cAMP: Cyclic adenosine monophosphate; CBAVD: Congenital bilateral absence of the vas deferens; CD: Celiac disease; CF: Cystic fibrosis; CFTR: Cystic fibrosis transmembrane conductance regulator; cGMP: Cyclic guanosine monophosphate; COPD: Chronic obstructive pulmonary disease; CREB: cAMP response element-binding protein; CTRC: Chymotrypsinogen C; ERK: Extracellular-regulated kinase; FEV1: Forced expiratory volume in 1 s; FSH: Follicle-stimulating hormone; HSP-90: Heat shock protein 90; ICP: Idiopathic chronic pancreatitis; JAK2: Janus kinase 2; miR: Reduced micro-RNA; MMP11: Matrix metalloproteinase 11; NBD1: Nucleotide-binding domain-1; NFKBIA: NF-κB inhibitor alpha; NF-Kb: Nuclear factor kappa-light-chain-enhancer of activated B cells; OR: Odds ratio; PCOS: Polycystic ovarian syndrome; PP2A: Protein phosphatase 2A; PRSS1: Cationic trypsinogen gene; PSC: Primary sclerosing cholangitis; SPINK: Serine peptidase inhibitor; STAT3: Signal transducer and activator of transcription-3; TGM2: Tissue transglutaminase 2; Upa: Urokinase plasminogen activator; VEGF: Vascular endothelial growth factor; VIP: Vasoactive intestinal peptide; WNK: With-no-lysine K.

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Consent for publication

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Competing interests

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