

Cite this: *RSC Med. Chem.*, 2025, 16, 3416

# The relationship between cancer risk and cystic fibrosis: the role of CFTR in cell growth and cancer development

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Cystic fibrosis (CF) is a life-limiting genetic disease that affects multiple organ systems. It is caused by a mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which results in the absence or damage of a relevant protein. If left untreated, it causes death in early childhood. The advent of more efficacious treatments has resulted in a notable increase in the life expectancy of CF patients. This has, in turn, led to an elevated risk of developing specific types of cancer. This review commences with an examination of CF from the standpoint of its etiology and therapeutic modalities. Subsequently, it presents a list of epidemiological studies that suggest an altered predisposition to certain cancers. A heightened risk is well documented, particularly in relation to the gastrointestinal tract. The following section addresses the role of CFTR in view of its potential involvement in the progression of various types of cancer. Several studies have indicated that the levels of the CFTR protein are reduced in many tumors and that this reduction is associated with the progression of the tumors. These decreased expressions are known to occur in the gastrointestinal tract, lungs, bladder, and/or prostate cancer. Conversely, ovarian, stomach, and cervical cancer are connected with its higher expression. The final section of the review focuses on the molecular mechanism of action of the CFTR protein in signaling pathways that affect cell proliferation and the process of carcinogenesis. This section attempts to explain the increased predisposition to cancer observed in patients with CF.

Received 6th March 2025,  
Accepted 17th May 2025

DOI: 10.1039/d5md00203f

rsc.li/medchem

## 1. Introduction

Cancer is a generic term for a large group of diseases that can affect any part of the body and is a leading cause of death worldwide. It is a genetic disease characterized by uncontrolled proliferation. The etiology of cancer is notably multifaceted, and its pathogenesis is complex, stemming from a combination of genetic, environmental, and lifestyle influences. In the midst of this complexity, emerging evidence suggests intriguing connections between cancer susceptibility and certain genetic disorders, offering novel insights into the molecular mechanisms underlying both malignancies and hereditary diseases. One such convergence is evident in the relationship between cancer and cystic fibrosis (CF), a hereditary disorder primarily characterized by dysfunction in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Age is a significant determinant in the development of cancer, with incidence rates increasing notably in older populations. The advent of therapeutic interventions has substantially prolonged the lifespan of cystic fibrosis (CF) patients, resulting in a demographic shift towards an older

patient population. While this increased longevity represents a positive clinical outcome, it concurrently introduces new concerns, including an elevated risk of cancer. One of the earliest studies examining the association between cancer risk and cystic fibrosis (CF) revealed a positive correlation between digestive tract tumors and CF, with an odds ratio of approximately 6.5.<sup>1</sup> A subsequent, more extensive investigation revealed that the standardized incidence ratio (SIR) of digestive tract cancer was 3.5, which increased to 17.3 in transplant patients.<sup>2</sup> Subsequent studies have corroborated the heightened cancer risk observed in CF patients, extending beyond the digestive tract to other organ systems. For a more thorough examination of this topic, please refer to chapter 2.2 of this review.

Although prior studies have examined the relationship between CF and primarily gastrointestinal malignancies, particularly colorectal cancer, a substantial gap in understanding remains concerning the broader role of CFTR in regulating cellular growth, proliferation, and tumor suppression across various tissue types. Moreover, the accelerated evolution and widespread implementation of CFTR modulators give rise to pivotal inquiries concerning their long-term ramifications for cancer risk, a subject that remains predominantly unaddressed in extant literature.

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The present review aims to address these knowledge gaps by providing a focused and contemporary analysis of the relationship between CFTR function and cancer risk. The objectives of this study are twofold: first, to examine the molecular mechanisms through which CFTR may influence carcinogenesis; and second, to examine the context-dependent effects of CFTR expression across different tumor types. In doing so, this review offers a timely and comprehensive synthesis of current evidence, identifies unresolved questions, and outlines directions for future research at the intersection of cystic fibrosis and oncology.

## 2. Cystic fibrosis

Cystic fibrosis is a life-limiting genetic autosomal recessive disease that affects multiple organ systems, primarily the respiratory, digestive, and reproductive ones.<sup>3</sup> When CF was first described in 1938,<sup>4</sup> it was a universally fatal disease of early childhood. The hereditary nature of CF was first demonstrated by Anderson, who published a pedigree analysis of CF in 20 affected families.<sup>5</sup> The disease is usually diagnosed in early childhood with typical symptoms. The diagnosis of CF usually begins with newborn screening to detect elevated levels of immunoreactive trypsin.<sup>6</sup> This is followed by genetic testing and, finally, sweat testing to measure the concentration of chloride ions in sweat.<sup>7</sup> Early diagnosis is critical for effective management of CF, as early intervention can help slow down the progression of the disease and improve long-term outcomes.

The molecular basis of CF was not described until 1989, when the gene responsible for the disease was identified and named the *cystic fibrosis transmembrane conductance regulator* (as well as its protein product).<sup>8–10</sup> CFTR is a member of the ATP-binding cassette (ABC) subfamily C (ABCC7).<sup>11</sup> CFTR is primarily expressed in the epithelial cells of the respiratory, digestive, and reproductive systems, where it plays a crucial role in maintaining proper hydration and pH balance of the body's fluids. As a chloride channel protein, it is a critical component in the regulation of ion and water transport across epithelial cells in various tissues.<sup>12</sup> However, it also serves as a bicarbonate,<sup>13</sup> thiocyanate,<sup>14</sup> and glutathione<sup>15</sup> channel. In addition, CFTR interacts with and regulates the activity of other ion channels and transporters, including the epithelial sodium channel (ENaC)<sup>16</sup> and the calcium-activated chloride channel (CaCC).<sup>17</sup> There is also a functional coupling between CFTR and multidrug resistance-associated protein 2 (MRP2).<sup>18</sup>

Additionally, more than 2000 mutations have been identified in the *CFTR* gene,<sup>19</sup> with varying degrees of severity in terms of their impact on protein function.<sup>20</sup> Variants can be classified into different functional classes based on their impact on the protein's function. Currently, the mutations are divided into seven groups.<sup>21</sup> Around two-thirds of the mutations found in CF patients are Class II mutations, which result in the creation of misfolded proteins that prevent them from moving to the cell surface.<sup>22</sup> This class also encompasses

the most prevalent mutation in the *CFTR* gene, namely the deletion of three base pairs that results in the loss of the amino acid phenylalanine at position 508 (referred to as F508del).<sup>23,24</sup> Homozygous F508del patients have an almost complete loss of the protein at the apical membrane.<sup>25</sup>

The most serious complications of CF are chronic lung diseases, which are the most common cause of death in CF patients.<sup>23,24</sup> Patients' lungs are most often colonized by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Burkholderia cepacia* and *Haemophilus influenzae*.<sup>23,24</sup> Other typical manifestations of cystic fibrosis are disorders within the gastrointestinal tract, where patients often suffer from a deficiency of pancreatic secretions and associated general malnutrition.<sup>26–29</sup>

### 2.1. Cystic fibrosis treatment

The therapeutic approaches to CF have predominantly involved mitigating symptomatic manifestations (symptomatic treatment). Contemporary interventions also focus on targeting the etiological origins of the disease, specifically the aberrant chloride channel (causal treatment).

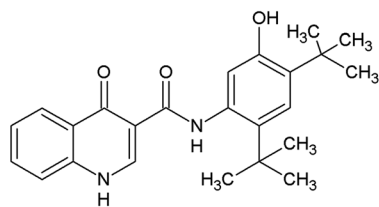
Symptomatic treatment focuses on managing the respiratory and digestive complications associated with CF. In the realm of respiratory care, airway clearance techniques, inhaled medications, and antibiotics play pivotal roles.<sup>30</sup> Mucolytics (e.g. amiloride, dornase alfa) help to reduce the viscosity and elasticity of mucus and increase its hydration.<sup>31,32</sup> Inhaled bronchodilators aid in dilating air passages, facilitating improved airflow. Moreover, antibiotics (e.g., tobramycin, colistin, levofloxacin, and sulfamethoxazole) combat bacterial infections that frequently afflict CF patients, preventing exacerbations and preserving lung function.<sup>33,34</sup> In really serious situations (chronic lung infection and subsequent destruction of lung tissue), lung transplantation is necessary. The digestive aspect of symptomatic treatment is based on pancreatic enzymatic replacement therapy (PERT) and nutritional interventions. PERT involves the supplementation of pancreatic enzymes to enhance digestion and nutrient absorption.<sup>35</sup> Nutritional support, including a high-calorie diet and fat-soluble vitamin supplementation, is crucial for maintaining optimal body weight and preventing malnutrition.<sup>36,37</sup>

On the causal front, recent breakthroughs in precision medicine have revolutionized CF treatment. Highly effective modulator therapies directly target the underlying genetic defect, enhancing the function of the defective CFTR protein. CFTR modulators include potentiators, which promote channel opening; correctors that correct defects in CFTR protein synthesis and functioning; and amplifiers, which increase the amount of CFTR protein that the cell produces by stabilizing CFTR mRNA.<sup>3,38,39</sup>

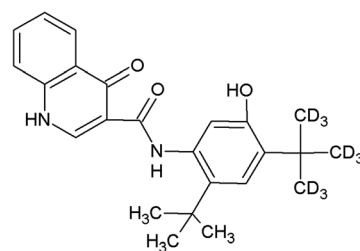
Presently, there are six CFTR modulators that are in clinical use. Two of these modulators, ivacaftor and deutivacaftor, are classified as potentiators (Fig. 1A). The remaining modulators, namely lumacaftor, tezacaftor,



A

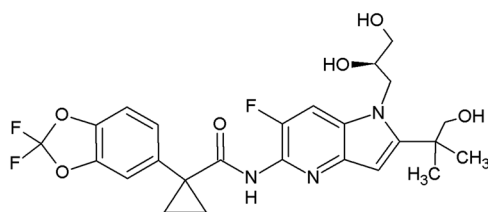


Ivacaftor

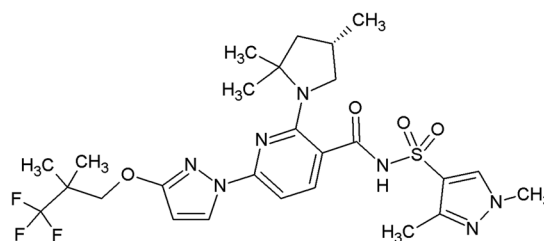


Deutivacaftor

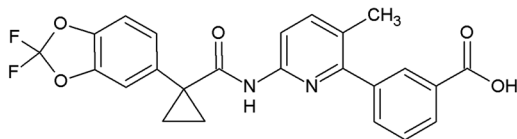
B



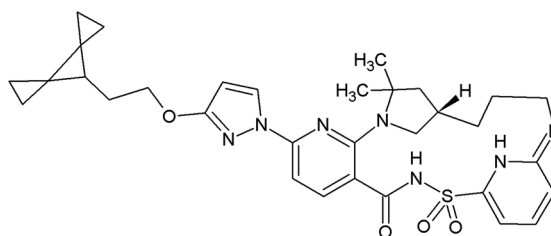
Tezacaftor



Elexacaftor



Lumacaftor



Vanzacaftor

Fig. 1 Chemical structures of approved modulators. A) Potentiators B) correctors.

elxacaftor, and vanzacaftor, are classified as correctors (Fig. 1B). However, even with correctors, only a proportion of the CFTR proteins reach the cell surface and function adequately. Consequently, correctors are utilized in conjunction with potentiators to enhance the therapeutic effect. The first approved modulator was ivacaftor, also known as Kalydeco, which functions as a CFTR potentiator authorized primarily for G551D and several additional gating mutations. However, it is ineffective for the prevalent F508del mutation due to reduced protein availability. Consequently, other approved modulator therapies are combinations of potentiators and correctors, which are also effective for the F508del mutation. These combination therapies include lumacaftor/ivacaftor (Orkambi),<sup>40</sup> tezacaftor/ivacaftor (Symdeko in the US and Symkevi in the EU),<sup>41</sup> elxacaftor/

tezacaftor/ivacaftor (Trikafta in the US, Kaftrio in the EU),<sup>42</sup> and the most advanced targeted therapeutic, vanzacaftor/tezacaftor/deutivacaftor (Alyftrek).<sup>43</sup>

A multitude of long-term clinical trials have been conducted to assess the safety and efficacy of CFTR modulators. These trials have consistently demonstrated that these therapeutic interventions are well tolerated and associated with sustained improvements in pulmonary function, nutritional status, and quality of life, along with a reduction in pulmonary exacerbations.<sup>44,45</sup> The restoration of CFTR function by modulators has been demonstrated to normalize epithelial ion transport and reduce inflammation.<sup>46</sup> Furthermore, ivacaftor has been demonstrated to exhibit a synergistic effect with osimertinib in the context of acquired resistance to osimertinib in non-small cell lung cancer.<sup>47</sup>



Although CFTR modulators represent a breakthrough, their efficacy is not universal. More than 10% of CFTR mutations do not produce any CFTR protein for CFTR modulators to act upon, which has rekindled great interest in the development of CFTR mutation-independent corrective strategies, including nucleic acid-based therapies such as RNA- or DNA-based interventions, as well as cell-based therapies or gene editing technologies.<sup>48–50</sup>

## 2.2. Risk of cancer in CF patients

In most countries with well-established CF care, adults now outnumber children, and life expectancy is expected to increase further, narrowing the survival gap with the general population.<sup>51</sup> As individuals with CF live longer, they are at an elevated risk of developing complications such as chronic lung disease, diabetes,<sup>52</sup> and osteoporosis.<sup>53,54</sup> With increasing survival, a predisposition to cancer, previously obscured by the short life span of these patients, may become evident. In the early 1990s, the study of cancer risk in patients with cystic fibrosis was initiated due to several reported cases of cancer in CF patients by the 1980s.<sup>1,55–57</sup> These studies indicated that the overall risk of cancer in patients with cystic fibrosis is like that of the general population, although there is an increased risk of digestive tract cancers with an odds ratio  $\approx$  6.5.

Subsequent studies have been conducted to explore the link between cystic fibrosis and different types of cancer. Maisonneuve *et al.* conducted one of the first large-scale studies that followed 41 188 patients who received care at CF care center programs in the United States from 1990 to 2009.<sup>2</sup> The study compared the observed number of cancers with that expected in the general US population. The overall cancer risk of CF patients was similar to the background risk of the general population. However, an increased risk was observed not only for digestive tract cancer (SIR = 3.5), but also for testicular cancer (SIR = 1.7), and lymphoid leukemia (SIR = 2.0). The study also examined the effects of lung transplantation. In patients with cystic fibrosis who have undergone a transplant, there was an elevated risk observed for overall cancer incidence (SIR = 2.7). The highest risk was observed for digestive organs (SIR = 17.3).

Using data from the transplant cancer match study confirmed the increased risk in CF patients after transplant (SIR = 9.9).<sup>58</sup> In addition, the risk of colorectal cancer (SIR = 24.2), esophageal cancer (SIR = 56.3), and non-Hodgkin lymphoma (NHL; SIR = 61.8) was significantly higher in CF recipients than in non-CF recipients. The risk of colorectal cancer was significantly higher among CF recipients than in the general population, as well as higher than among non-CF recipients, for all subsites of the colorectum (proximal colon, distal colon, and rectum).<sup>58,59</sup> Additionally, the most common types of cancer also differ between these two groups. The most common cancers among CF recipients were NHL (40% of the total) and colorectal cancer (18%). For non-CF recipients, the most common cancers were lung cancer

(25%) and NHL (17%).<sup>58</sup> The recipients with cystic fibrosis (CF) and those without differ not only in terms of cancer diagnosis but also in their age. Among CF recipients, 77% were younger than 35 years of age, whereas this figure was only 7% among non-CF recipients.<sup>58</sup> Recent investigations, including a study on cancer rates in CF patients with and without lung transplants conducted by Rousset-Jablonski *et al.* in France, confirmed a higher incidence of cancer in both non-transplanted (SIR = 2.57) and transplanted (SIR = 19.76) patients compared to the general population.<sup>60</sup> There was a significantly higher number of colorectal cancer and of lung cancer in non-transplanted CF patients than in the general population. Among transplanted CF patients significantly higher number was observed not only for colorectal and lung cancer but also for several others, including small intestine, kidney, and bladder cancer. Yamada *et al.* determined the pooled incidence rate of gastrointestinal cancers to be 79 per 100 000 for CF individuals per year. The incidence rates for small bowel, colon, biliary tract, and pancreatic cancer were 13, 39, 5.1, and 5.8 per 100 000 CF individuals per year, respectively.<sup>61</sup>

CF-related diabetes and homozygous  $\Delta$ F508 mutation are statistically significant risk factors that are associated with polyp formation.<sup>62</sup> Endoscopic studies have revealed that adenomatous polyps were detected on initial screening colonoscopies in 49% CF patients over the age of 40. In addition, patients with negative initial examinations had undergone follow-up re-screening within a mean period of 49 months, and 47% re-screening examinations revealed adenomas.<sup>62</sup> In response to these findings, recommendations have been proposed and published.<sup>63</sup> Following these recommendations, it is estimated that more than 66% of colorectal cancer deaths among individuals with cystic fibrosis and 39% of individuals with cystic fibrosis post-transplant can be prevented.<sup>64</sup> In addition to polyp formation, CF is also associated with an increased risk of development of gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), or related neoplasia.<sup>65</sup>

Additionally, research has indicated a potential correlation between cystic fibrosis (CF) and an elevated risk of breast cancer<sup>66</sup> or gynecological malignancies, including cervical intraepithelial neoplasia and cervical cancer, in individuals with this condition.<sup>67</sup>

It is evident that, although the cancer risk varies between screening studies, a higher risk of GIT cancer and a higher risk after transplantation are common to all studies. Variations in population demographics and other unaccounted factors, such as diet or environment, may also play a role in individual differences in cancer risk. Another potential explanation for the statistically significant elevated risk for specific types of cancer may be the repeated exposure of individuals with CF to X-ray examinations at an early age.<sup>68</sup> While numerous studies have indicated that routine annual CT scans in patients with CF pose a minimal risk of radiation-induced cancer,<sup>69</sup> there are potential associations with specific types of cancer.<sup>68</sup>



Also, immunosuppression after lung transplantation, chronic inflammation, and long-term use of antibiotics may all contribute to cancer risk. Immunosuppression is a known risk factor of cancer even in non-cystic fibrosis patients.<sup>70,71</sup> Immunosuppressants compromise immune surveillance, enabling premalignant cells and oncogenic viruses such as Epstein–Barr virus (EBV) and human papillomavirus (HPV) to evade host control.<sup>72</sup> Chronic inflammation contributes to tumorigenesis by generating a pro-oncogenic microenvironment rich in cytokines, growth factors, and reactive oxygen species (ROS), which collectively drive proliferation, inhibit apoptosis, and induce DNA damage.<sup>73–75</sup> Sustained activation of pathways such as TGF- $\beta$ , NF- $\kappa$ B, and STAT3 promotes tissue remodeling and genomic instability, facilitating malignant transformation, angiogenesis, and immune evasion.<sup>73,74</sup> Additionally, long-term antibiotic exposure can disrupt mucosal microbial communities, reducing protective taxa (*e.g.*, Bacteroidetes) and enriching pro-carcinogenic species (*e.g.*, *Fusobacterium*) across barrier sites such as the gut and lungs. This dysbiosis impairs mucosal immunity, sustains low-grade inflammation, and facilitates the production of genotoxic microbial metabolites.<sup>76,77</sup>

### 2.3. Risk of cancer in CFTR carriers

Although patients with cystic fibrosis (CF) are at increased risk of some cancers, little is known about the cancer risks among their first-degree relatives and CF carriers, subjects carrying only one defective copy of the CFTR gene. Although cystic fibrosis is rare, approximately 4–5% of the Caucasian population are heterozygous mutation carriers of the CFTR gene. One theory for this high incidence of CFTR mutation carriers in the population is that these carriers may have some biological advantage. One such advantage is likely to be higher resistance to tuberculosis.<sup>78</sup> However, there may be other benefits. Such benefits may include heightened resistance to infectious diseases such as cholera,<sup>79</sup> or *Salmonella typhi*.<sup>80</sup> Some studies suggest that CFTR carriers may have lower risks of melanoma,<sup>81,82</sup> colorectal cancer,<sup>82</sup> prostate cancer,<sup>83</sup> or breast cancer.<sup>82,84</sup> However, the reduced risk of breast cancer was not statistically significant,<sup>82</sup> and a subsequent study even suggested the opposite.<sup>85</sup> Taken together, these results indicate that there may be an altered level of cancer risk in CFTR carriers.

A study tracking the parents and siblings of 884 CF patients yielded no association with overall cancer risk among these individuals, although in the site-specific analyses a significant increased risk of esophageal cancer among the parents was observed.<sup>86</sup> Moreover, a recent large study found that CF carriers had a statistically significant higher prevalence of 57 CF-related conditions compared to controls. These conditions include, among other cancers of the digestive organs and pancreatic cancer.<sup>87</sup> Previous studies have shown that carrying a germline mutation in CFTR only slightly increases the risk of pancreatic adenocarcinoma.<sup>88,89</sup> Mutation carriers also appear to be diagnosed at a younger

age than non-carriers, with this effect seen exclusively among ever smokers.<sup>88</sup> However, the different mutations present varying levels of cancer risk.<sup>89</sup>

Another study investigating the risk of cancer in cystic fibrosis F508del carriers was published in 2021 and analyzed 54 types of cancer. Compared to non-cancer subjects, the carrier rate of CFTR F508del was significantly higher in four types of cancers: colorectal cancer, cancers of the gallbladder and biliary tract, thyroid cancer, and unspecified non-Hodgkin's lymphoma. Although the rate of pancreatic cancer was also increased in CFTR F508del carriers, the difference was not statistically significant.<sup>90</sup> In contrast, the carrier rate in patients with lung and bronchus cancer was significantly lower.<sup>90</sup> Similar results were previously obtained in experiments at the Mayo Clinic (Rochester, Minnesota) showing that carriers of the  $\Delta$ F508 deletion, as well as carriers of some single nucleotide polymorphisms, have a lower risk of lung cancer than non-carriers.<sup>91</sup> On the contrary, Çolak *et al.* analyzed white Danish individuals from the Copenhagen general population study and found that the carriers of the F508del mutation have an increased risk of lung cancer, chronic bronchitis, and bronchiectasis.<sup>92</sup>

On the basis of these results, we can conclude that cancer risk is changed in CF carriers in comparison to noncarriers and that the form of CFTR mutation may play an important role in this change.

## 3. Role of CFTR in hyperplasia and cancer

As discussed in the previous chapter, individuals with CF or who are CFTR carriers may demonstrate an altered susceptibility to the development of malignant neoplasms. This suggests that the CFTR protein may be involved in cellular processes that regulate cell proliferation. It is therefore plausible that alterations in its expression may be observed in tumors of the general population. Indeed, there are tumors with both lower and higher expression of CFTR.

### 3.1. Tumors with lower expression of CFTR

Numerous studies have suggested that CFTR acts as a tumor suppressor gene.<sup>93,94</sup> This may provide a potential explanation for the observed association between tumor formation and reduced expression of CFTR in several organs and tissues, including lungs or colon.

For instance, non-small cell lung cancer (NSCLC) exhibited statistically significant lower levels of CFTR transcripts in comparison to normal lung tissue. The lower expression of CFTR in NSCLC tissues is associated with promoter hypermethylation. This phenomenon is more frequently observed in tissues from patients with squamous cell carcinoma than in those with adenocarcinoma.<sup>95</sup> Moreover, patients with low CFTR levels generally had more advanced tumors, and low CFTR gene expression correlates with poor prognosis independent of clinical stages.<sup>96,97</sup> The



alteration of *CFTR* expression did not significantly affect the proliferation of two lung adenocarcinoma cell lines, A-549 (ref. 96) and Calu-3.<sup>98,99</sup> Therefore, it is unlikely that cell proliferation is affected by the alteration of *CFTR* expression. However, the study by Li *et al.* found that knockdown of *CFTR* significantly enhanced cell invasion and migration, which may explain the poorer prognosis associated with lower *CFTR* expression.<sup>96</sup>

The *CFTR* expression is also found significantly downregulated in primary human breast cancer samples and is closely associated with poor prognosis in different cohorts of breast cancer patients.<sup>100</sup> The decrease in *CFTR* levels in breast cancer is also caused by methylation, as the *CFTR* promoter has higher methylation levels in breast cancer compared to normal tissue.<sup>101</sup> Than *et al.* found that the loss of *CFTR* alters the expression of several genes in the colon and small intestine.<sup>93</sup> A meta-analysis of three datasets supports the hypothesis that lower *CFTR* expression is associated with poorer prognosis and increased colorectal cancer (CRC) mortality.<sup>102</sup> CRC is therefore another diagnosis associated with lower expression of *CFTR*, likely due to promoter methylation.<sup>94</sup> Additionally, hypermethylation was observed in patients with hepatocellular carcinoma,<sup>103</sup> bladder cancer<sup>104</sup> and prostate cancer.<sup>105</sup> Hypermethylation is also seen in A253 head and neck carcinoma cells derived from human submandibular gland tumors and in head and neck carcinoma tissue samples.<sup>106</sup>

Furthermore, reduced *CFTR* expression in nasopharyngeal carcinoma (NPC) cell lines and tissues is correlated with poor prognosis and inferior survival. *CFTR* also affects the migration and invasion abilities of NPC cell lines.<sup>107</sup> A similar trend is observed in esophageal squamous cell carcinoma (ESCC), where *CFTR* expression is found to be downregulated, contributing to the regulation of cell proliferation, migration, and invasion. All of these properties are higher with lower *CFTR* expression. Thus, the weak expression of *CFTR* is a significant poor prognostic factor for ESCC patients.<sup>108</sup> However, nothing is known about methylation of *CFTR* promoters in these cell lines.

In conclusion, the expression of *CFTR* is often reduced as a result of epigenetic processes, frequently associated with promoter hypermethylation, which ultimately lead to the transcriptional silencing of the gene. The absence of functional *CFTR* or its lower expression is associated with the activation of epithelial–mesenchymal transition (EMT).<sup>100,109</sup> EMT is characterized by the loss of epithelial cell traits and the acquisition of a mesenchymal-like phenotype, facilitating cellular invasion into surrounding tissues and metastasis to distant sites. This correlation highlights the potential of *CFTR* as a valuable biomarker for cancer prognosis and a promising target for therapeutic interventions.

### 3.2. Tumors with higher expression of *CFTR*

In contrast to tumors with lower levels of *CFTR* expression, which is often associated with

hypermethylation, the underlying cause(s) for the higher levels of expression remain unknown. Cancers with higher levels of *CFTR* expression include cervical, ovarian, and gastric cancers.

The expression of *CFTR* in ovarian cancer specimens was significantly higher than that in benign and normal ovaries. The *CFTR* protein level was well-related to advanced clinical stages and poor histological grade. The lower expression of *CFTR* has been linked to the inhibition of cell motility, invasion, and proliferation in epithelial ovarian cancer cell lines, suggesting that *CFTR* knockdown suppresses tumor progression.<sup>110</sup> In gastric cancer, a strong positive correlation was observed between *CFTR* expression and stage in serum samples from 78 patients. The serum level of *CFTR* was significantly higher in gastric cancer patients than in healthy controls.<sup>111</sup> In the case of cervical cancer, *CFTR* mRNA and protein expression gradually increase from normal to cervical cancer tissues. *CFTR* expression was well correlated to tumor stage, histological grades, lymphatic metastasis, vascular invasion, interstitial invasive depth, and tumor size<sup>112</sup> with *CFTR* mutation and *CFTR* promoter methylation not contributing to cervical cancer development.<sup>113</sup> Nevertheless, the findings indicate that elevated *CFTR* expression is associated with the NF- $\kappa$ B signaling pathway. NF- $\kappa$ B has been demonstrated to possess the capacity to activate transcription and augment *CFTR* expression. Conversely, *CFTR* has been shown to exert a feedback inhibitory effect on NF- $\kappa$ B.<sup>113</sup> Therefore, an elevated level of *CFTR* protein in cervical cancer is the consequence of NF- $\kappa$ B signaling pathway activation and inadequate feedback inhibition. When NF- $\kappa$ B is active, it leads to increased expression of *CFTR*. However, *CFTR* protein itself does not sufficiently inhibit NF- $\kappa$ B signaling. NF- $\kappa$ B activation is also associated with gastric<sup>114,115</sup> and ovarian cancer.<sup>116</sup> However, there's no info about the relation to the *CFTR* protein, but its increased expression in these cancers may be due to absent feedback inhibition, as is the case in cervical cancer. *CFTR* is also highly expressed in acute lymphoblastic leukemia.<sup>117,118</sup>

## 4. Molecular mechanism of *CFTR* in cell proliferation

As illustrated in the preceding section, individuals with *CF* exhibit a heightened propensity for certain types of cancer while displaying a diminished susceptibility to others. Moreover, it is well documented that specific tumors exhibit alterations in the expression of *CFTR*. However, the relationship between cystic fibrosis and cancer is complex and encompasses a range of biological mechanisms, including disrupted ion transport, inflammation, dysregulated cellular signaling, and DNA damage response. The reason for the modified susceptibility can be attributed to the molecular mechanisms through which various signaling pathways are affected.



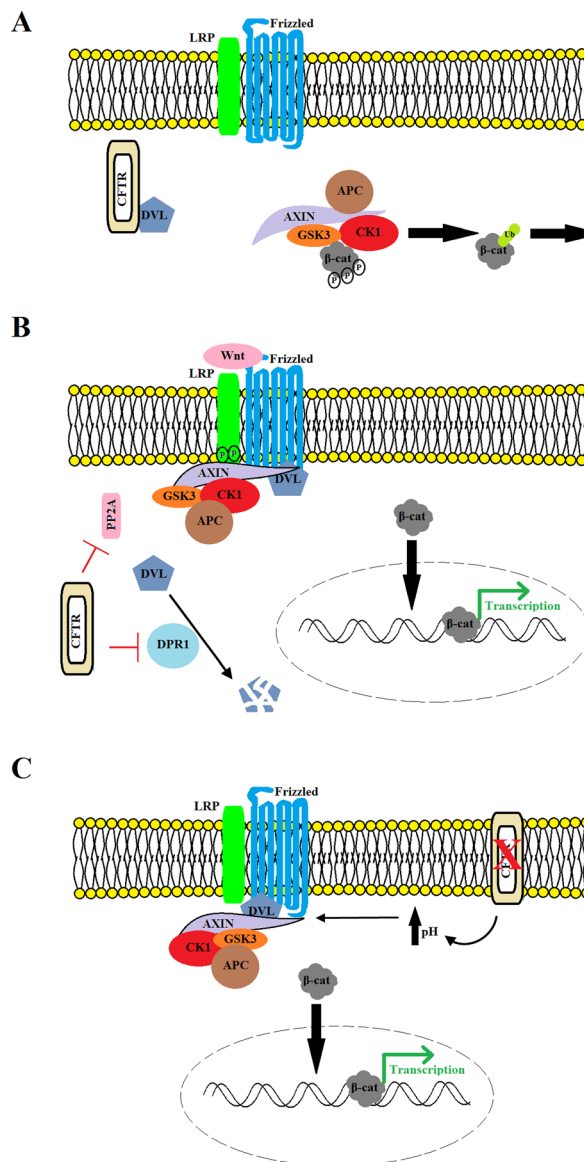
#### 4.1. Wnt/ $\beta$ -catenin signaling pathway

The Wnt/ $\beta$ -catenin signaling pathway, a highly conserved pathway in insects, mammals, and other species, is pivotal in regulating fundamental physiological and pathological processes such as cell proliferation and differentiation, programmed cell death, or cell migration. Wnt proteins activate three signaling pathways: the canonical or  $\beta$ -catenin pathway and two  $\beta$ -catenin-independent, non-canonical pathways. To date, eight canonical gene elements associated with Wnt/ $\beta$ -catenin signaling have been described. For further information, please refer to the following sources: ref. 119 and 120.

One of the mechanisms by which CFTR affects Wnt/ $\beta$ -catenin signaling is through a direct interaction between scaffold proteins disheveled 2 (Dvl-2) and CFTR (Fig. 2A). This interaction *via* the PDZ domain in Dvl-2 has been described in the kidney, where it negatively regulates  $\beta$ -catenin signaling. Thus, the dysfunction or downregulation of CFTR activates canonical Wnt/ $\beta$ -catenin signaling pathways, which in turn alter the expression of genes involved in epithelial-mesenchymal transition (EMT).<sup>121</sup> Furthermore, direct interaction between CFTR and Dvl-2 has been linked to the anemic phenotype observed in patients with cystic fibrosis. However, in this case CFTR regulates  $\beta$ -catenin positively, and the channel function is not necessary<sup>122</sup> (Fig. 2B). The reduction of CFTR protein level has been found to impact canonical Wnt/ $\beta$ -catenin signaling by downregulating Dvl-2 and  $\beta$ -catenin while upregulating p-GSK3 $\beta$  in Philadelphia chromosome-positive acute lymphoblastic leukemia. These effects are mediated through the interaction between CFTR and protein phosphatase 2A (PP2A) in the cytosol, resulting in the inactivation of the PP2A complex,<sup>117</sup> and the inhibition of GSK-3 activity due to phosphorylation of Ser/Pro-rich sequences present in the Wnt co-receptors LRP5/6 (ref. 123 and 124) (Fig. 2B).

Another mechanism observed in CF mouse models suggests that the absence of CFTR leads to an increase in intestinal epithelial intracellular pH (Fig. 2C). This increase stabilizes the plasma membrane association of Dvl-2, which likely facilitates Wnt/ $\beta$ -catenin signaling.<sup>125</sup> In contrast, the study examining inflammation in the  $\Delta F508$  CFTR mouse small intestine concluded that loss of CFTR activity suppresses active  $\beta$ -catenin signaling.<sup>126</sup> The authors explained the methodological reasons for the discrepancy between the experiments. One experiment used only epithelial cells, while the other experiment employed both epithelial and non-epithelial cells. The positive correlation between CFTR and  $\beta$ -catenin protein level is explained by a direct interaction between CFTR and  $\beta$ -catenin, where CFTR protein prevents the degradation of  $\beta$ -catenin.<sup>126</sup> The same was also observed in mouse embryonic stem cell differentiation and embryonic development experiments.<sup>127</sup>

It has also been demonstrated that  $\beta$ -catenin exerts a regulatory influence on the hedgehog signaling pathway.



**Fig. 2** The impact of the cfr protein on the  $\beta$ -catenin signaling pathway in kidney epithelial cells (A) and intestinal non-epithelial (C) cells and epithelial cells (B) is illustrated. In kidney epithelial cells (A), the interaction of cfr with Dvl-2 has been demonstrated to result in the activation of the destruction complex and the subsequent degradation of  $\beta$ -catenin. In non-epithelial cells (B), the interaction of CFTR protein with phosphoprotein phosphatase results in its deactivation. Consequently, the destruction complex is inactivated through the interaction with phosphorylated LRP, which allows  $\beta$ -catenin to be transported into the nucleus. Furthermore, CFTR has been shown to inhibit DPR1, which promotes the ubiquitination of Dvl2. This, in turn, may inhibit the destruction complex. In intestinal epithelial cells (C), a reduction in the functionality of the cfr protein consequently leads to an increase in intracellular pH, which stabilises the interaction between the wnt receptor and Dvl-2 and thus inhibits the destruction complex.

Experiments on mice have indicated that the  $\Delta F508$  mutation and downregulation of CFTR result in hyperproliferation of the small intestine and intestinal epithelial cell lines as well as the inhibition of enterocyte maturation.<sup>128</sup> The expression of several proteins related to the hedgehog signaling



pathway, including Indian-hedgehog (Ihh), patched (Ptch), and glioma-associated oncogene transcription factor Gli1, has been observed to change, leading to hedgehog signaling suppression.

#### 4.2. NF- $\kappa$ B pathway

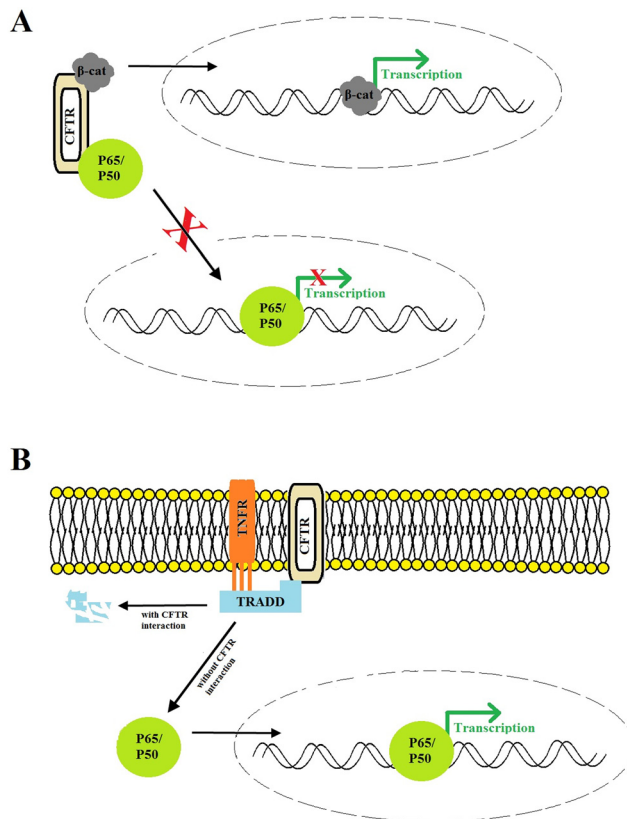
The NF $\kappa$ B (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling pathway plays a crucial role in regulating various cellular processes, such as inflammatory responses, innate and adaptive immunity, as well as cellular differentiation, proliferation, and survival in almost all multicellular organisms. In *Mammalia*, the NF- $\kappa$ B network consists of five family member protein monomers (p65/RelA, RelB, cRel, p50, and p52) that form homodimers or heterodimers and are regulated by two pathways: the canonical and the noncanonical pathways. It is postulated that 12 of the 15 potential dimers can bind the DNA  $\kappa$ B element. Of the 12 DNA-binding dimers, nine contain at least one of the activator proteins and typically function as transcriptional activators.<sup>129</sup> For further information regarding the canonic pathway, refer to, ref. 130 while ref. 131 provides insights into the non-canonic pathway.

CFTR is known to act as a negative regulator of NF- $\kappa$ B-mediated inflammation.<sup>128,132–134</sup> Data indicates that CFTR has anti-inflammatory properties and that the hyperinflammation found in CF is in part due to a disruption of the signaling link between CFTR and NF- $\kappa$ B.<sup>132,133</sup> Additionally, CFTR regulates the cyclooxygenase 2 (COX2)/prostaglandin E2 (PGE2) pathway.<sup>135–137</sup> For example, the down-regulation of CFTR, which subsequently activates the NF- $\kappa$ B/COX2/PGE2 pathway during aging, contributes to benign prostatic hyperplasia.<sup>136</sup>

One way of CFTR effect on the NF- $\kappa$ B pathway is through  $\beta$ -catenin signaling (Fig. 3A).  $\beta$ -Catenin inhibits NF- $\kappa$ B activity and is able to complex with p65 and p50, although additional cellular factors are required.<sup>138</sup> CFTR may be one of these factors, as studies have shown its interaction with  $\beta$ -catenin and p65 in Caco-2 cells and mouse small intestine.<sup>126</sup> Defective CFTR- $\beta$ -catenin interaction promotes NF- $\kappa$ B nuclear translocation.<sup>126</sup> CFTR also inhibits the expression of NF- $\kappa$ B p50 and NF- $\kappa$ B p65 in esophageal cancer cells.<sup>139</sup> Similarly, CFTR inhibits the expression of NF- $\kappa$ B p65 in HeLa cells.<sup>113</sup>

Another way to regulate the NF- $\kappa$ B pathway is dependent on tumor necrosis factor receptor type 1-associated DEATH domain protein (TRADD) (Fig. 3B). It is known that overexpression of TRADD activates NF- $\kappa$ B.<sup>140</sup> The regulation of NF- $\kappa$ B activity by TRADD is contingent upon the interaction of TRADD with a functional CFTR. The interaction between CFTR and TRADD *via* the PDZ domain results in the degradation of TRADD in lysosomes.<sup>141</sup>

The expression of the CFTR and the NF- $\kappa$ B is observed to occur concurrently in cervical cancer. This is evidenced by the progressive increase in both NF- $\kappa$ B and CFTR mRNA and protein expression observed in the progression from normal cervical tissue to cervical cancer.<sup>112,142</sup>



**Fig. 3** The impact of CFTR on NF- $\kappa$ B is manifesting in two distinct ways. Firstly, CFTR interacts with  $\beta$ -catenin in small intestine or esophagus, stabilising it and thereby inhibiting the NF- $\kappa$ B pathway. In the absence or damage of CFTR protein, there is degradation of  $\beta$ -catenin and translocation of NF- $\kappa$ B into the nucleus (A). Secondly, the *cfr* protein interacts with TRADD, resulting in its subsequent degradation. Absent this interaction, TRADD activates the NF- $\kappa$ B pathway (B).

#### 4.3. Urokinase-type plasminogen activator pathway

The plasminogen activator (PA) system performs functions in a variety of biological processes, including embryogenesis, angiogenesis, cell migration, wound healing, and the inflammatory response. Moreover, it plays a pivotal role in tumor growth, angiogenesis, tumor cell invasion, migration, and metastasis.<sup>143</sup> The urokinase-type plasminogen activator (uPA) pathway consists of uPA, its receptor (uPAR), and plasminogen activator inhibitors (PAIs).<sup>144</sup> When uPA binds to uPAR, it initiates a proteolytic cascade that converts plasminogen to plasmin, which degrades extracellular matrix components and activates matrix metalloproteinases, facilitating tumor invasion and metastasis.<sup>144–146</sup>

Knockdown of CFTR increased the activity of the uPA pathway, while overexpression of CFTR inhibited it in NSCLC cell line A-549 cells.<sup>96</sup> Moreover, *in vivo* studies demonstrated that overexpression of CFTR can even impede lung metastasis of MDA-231 cells through uPA.<sup>100</sup> Overexpression of CFTR suppressed uPA as well as tumor progression *via* miR-193b in prostate cancer.<sup>147</sup> The downregulation of CFTR also increased epithelial-to-mesenchymal transition, cell migration and invasion of



colorectal cancer (CRC) cells by uPA.<sup>148</sup> The mRNA levels of CFTR were positively correlated with uPA receptor (uPAR) expression levels in the ovarian endometriotic lesions. In accordance with the observed mRNA expression, the protein levels of both CFTR and uPAR were found to be significantly elevated. The effect of CFTR on uPAR expression was determined to be through the activation of NFκB.<sup>149</sup>

#### 4.4. Other mechanism

In addition to the aforementioned mechanisms, there are also other mechanisms that link CFTR protein with cancer. One example is a correlation found between a lower expression of CFTR and AF-6/afadin and poor prognosis in colon cancer patients. CFTR physically interacts with AF-6/afadin, resulting in its enhanced degradation.<sup>150</sup> Afadin is a multi-domain scaffold protein commonly found in adherens and tight junctions, where it plays both structural and signal-modulating roles, such as signal transduction, migration, invasion, and apoptosis.<sup>151</sup> The suppression of AF-6/afadin has been shown to worsen malignant phenotypes in colon cancer cells through the activation of the ERK pathway.<sup>150</sup> Moreover, CFTR regulates phosphorylation of AKT and ERK1/2 and thus the expression of Bcl-2, Bax, and Bad in colorectal cancer. This regulation is caused by interaction between CFTR and Hsp90.<sup>152</sup> The impact of CFTR on MAP kinases is corroborated by another study demonstrating that CFTR modulates the functions of ESCC cells, including proliferation and survival, through the P38 MAPK signaling pathway.<sup>108</sup>

CFTR also exerts a negative regulatory effect on the expression of MUC4, a member of the membrane-bound mucin gene family, through both transcriptional and posttranslational mechanisms.<sup>153</sup> Higher expression of MUC4 is associated with tumor cell growth and metastasis, as MUC4 expression is not detectable at the RNA level in normal pancreas but is detectable at high levels in invasive pancreatic adenocarcinoma.<sup>154–157</sup>

## 5. Conclusion

The results of epidemiological studies provide compelling evidence that CF is associated with an elevated risk of specific types of cancer. This aforementioned risk, which was previously obscured due to the low life expectancy of individual CF patients, is becoming increasingly evident as the quality of care improves and, consequently, the life expectancy increases. This phenomenon is most evident in colon cancer, which is several times more prevalent than in a healthy individual, and the risk increases even more after lung transplantation. The elevated predisposition to neoplastic disease is presumably attributable to the expression of the CFTR protein, as the level of this protein is altered in a number of neoplasms where it is associated with progression. The reduction in CFTR protein expression has been observed in tumor types that are epidemiologically

increased in CF patients. Conversely, it may be hypothesized that CF patients may exhibit increased resistance against tumor types in which an increase in CFTR protein is observed. However, there are currently insufficient data to confirm this assumption. CFTR protein has been demonstrated to play a role in the development of cancer through its interaction with multiple signaling pathways that may also interact with one another. Furthermore, the specific nature of the mutations in CFTR appears to be a contributing factor to this process. The various mutations in CFTR exert different effects on the protein, consequently affecting cell signaling pathways in a distinct manner due to the variable interactions between the CFTR protein and proteins within these signaling pathways. Moreover, cystic fibrosis has been linked to the presence of inflammation, extended periods of antibiotic treatment, and, in more extreme cases, the necessity of lung transplantation. These three factors have been identified as risk factors for cancer. The utilization of CFTR modulators has been demonstrated to attenuate the likelihood of inflammation and transplantation. Consequently, these modulators may play a pivotal role in the reduction of cancer risk among individuals with CF. Therefore, a detailed understanding of the molecular basis of these complex cross-talks is important to understand the cancer process in CF patients and to introduce measures reducing the risk to the level of the healthy population.

In summary, this review underscores the intricate interplay between CFTR dysfunction and the development of cancer, emphasizing the heightened cancer risk observed in both CFTR patients and CFTR mutation carriers. A more profound comprehension of these intricate interactions could facilitate the development of targeted therapeutic strategies or the design of innovative prevention and screening programs, as well as enhance cancer treatment in individuals with CF and CFTR-related disorders. The utilization of modulators in the treatment of cystic fibrosis has been demonstrated to enhance patient well-being and, in our estimation, may potentially contribute to a reduction in cancer risk. This decline may be attributable to a decrease in inflammation and dysbiosis, as well as to the re-establishment of CFTR protein expression, which functions as a tumor suppressor gene. The potential for modulators to contribute to the treatment of cancers associated with low CFTR protein expression is predicated on the modulators' capacity to affect CFTR protein expression. This capacity is not exclusive to individuals suffering from cystic fibrosis; it may also extend to individuals who do not have this condition. The validity of our hypothesis is supported by a study demonstrating a synergistic effect of osimertinib on resistance in non-small cell lung cancer.

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.



## Author contributions

RI conceived the review concept, designed the figures, and drafted the initial manuscript, with the exception of chapter 2.1 and the introduction of chapter 2, which he revised. VČ prepared chapter 2.1 and the introduction of chapter 2 and undertook revisions to the remaining sections.

## Conflicts of interest

The authors declare no conflict of interest.

## Acknowledgements

This research received no specific grant from any funding agency, commercial or not-for-profit sectors. We would like to thank Prof. Petr Hodek and Dr. Božena Kubičková for revision of the manuscript.

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