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■ REVIEW ARTICLE

The Molecular Basis of Cystic Fibrosis

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ABSTRACT: Cystic Fibrosis is the most common autosomal recessive disorder that affects Caucasians. It is caused by a mutation of the expression of the CF transmembrane conductance regulator (*CFTR*) gene, which has over 2,500 noted variants, spawning irregular chloride channels in mucus and sweat-producing cells. The disease causes damage to the respiratory system and GI tract until the organs fail to function by causing thick mucus to build up in the lungs and pancreas. As the chronic disease currently has no cure, people with this condition can generally live normal lives, as many tools and techniques can be used to manage this complex condition. However, this does not mean that patients live perfectly healthy lives, as they still experience symptoms such as shortness of breath and coughing. This review article summarises the pathology and pathomechanism of the disease, what it is on a genetic expression level, and emerging therapies.

KEYWORDS: Cystic Fibrosis, CFTR, Bronchiectasis, Pancreatitis, Antisense oligonucleotides, Splice site mutations.

■ Introduction

Cystic Fibrosis (CF) is a deadly disease that affects 250,000 people worldwide[1] and is caused by the absence or malfunction of the chloride ion channel, CFTR.[2] This channel, located at the apical membrane of epithelial cells of the respiratory tract, sweat ducts, gastrointestinal tract, and reproductive organs, allows for anion flow to occur.[3] Under the absence of anion flow, water movement slows, and dehydrated mucus clogs ducts and collects in many exocrine organs, obstructing airways and eventually causing lethal bacterial infections.[2,4] Thus, the disease is primarily characterized by progressive deterioration of the lung and a high NaCl concentration in sweat.[5] Additionally, CF patients also face an increased incidence of gastrointestinal complications due to obstruction of pancreatic ducts, causing insufficient delivery of pancreatic enzymes, liver disease, and gallbladder disease.[4] Although the diagnosis of CF can be devastating, significant advancements in research have led to improvements in treatment options such as drug therapy, physiotherapy, and nutritional support.[6] Currently, drug therapy, extensive physiotherapy, and nutritional support are ways of treatment. Still, gene therapy, targeting of cellular interactions, and newer drugs for symptom management are promising with new technology and research.[7] Additionally, another option for these patients would be an organ transplant when the body stops responding to other therapies.[25] This review article summarises the pathology of CF, the pathomechanism of CF, what the disease is on a molecular level, and some future developing treatments. This article aims to provide a comprehensible piece of material for high school students through the use of complex jargon and the simplification of complex scientific ideas. As articles - whether it be review or research - analyzing the disease on a molecular level8, such as analysis of transcription factors[9], the chloride channels[2,5], and pathogenesis of the disease, use advanced scientific language often intangible for students. Moreover, the articles discussing currently available treatments are usually specific to a single or few treatments10, as opposed to a comprehensive overview of all up to the present that is summarised in one article.

Pathology and Pathomechanism of Cystic Fibrosis:

CF is caused by mutations in the *CFTR* gene on chromosome 7.[11] This gene codes for the CFTR protein, which functions as a transmembrane cyclic AMP (cAMP)-activated chloride channel that helps to maintain the balance of salt and water on certain epithelial cells in several organs, typically the skin, pancreas, and lungs.[11,12] It transports negatively charged chloride ions (Cl-) in and out of cells, regulating water movement across cell membranes in tissues.[13] In CF, the CFTR protein is defective, which disrupts the function of this chloride channel, resulting in an abnormal flow of chloride ions and water in and out of cells.[13] These mutations can result in either no CFTR protein being made or the malfunctioning of the protein.[14] The result of all mutations is the decreased secretion of chloride and, consequently, the increased sodium reabsorption, leading to increased water absorption, manifesting as thicker mucus secretions on epithelial linings and thicker secretions from exocrine tissues.[15] The most commonly affected organs are the sinuses, lungs, pancreas, biliary and hepatic systems, intestines, reproductive systems, and sweat glands.[15] The following sections will outline the structures and organs that are affected due to the disease.

Sinuses:

A majority of CF patients develop sinus symptoms at five to fourteen years old.[16] Sinus disease is a condition in which the fluid in the sinuses thickens and blocks the openings, and is often in association with other issues, such as problems with the hair-like structures that move mucus, increased inflammation, and an overgrowth of harmful bacteria.[15] This makes clearing the sinuses more difficult and can result in chronic sinusitis, leading to further damage to the structures.[15] Chronic Rhinosinusitis (CRS) is the most common complication of CF. It is observed in almost all cases of clinical CF.[17] Symptoms

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of CRS in CF include nasal obstruction, purulent rhinorrhea, facial pain or pressure, and hyposmia or anosmia.[17] Other sinus diseases associated with CF include acute and chronic sinusitis, compromised mucociliary clearance (MCC), and increased prevalence of chronic rhinosinusitis in carriers of CF mutations.[18-20]

Lungs:

The predominant cause of death in patients with CF is end-stage lung disease.[15,21] This is when mucus caused by CF blocks the airways (Figure 1), making it harder to move air in and out of the lungs and clear mucus from the bronchial tubes.[22] The lungs of a CF patient are normal inside the uterus at birth. After birth, the disease results from a cascade effect following infection and inflammatory processes.[15] Mucus plugging up in the bronchioles results in symptoms of obstructive lung disease, providing an environment optimal for bacterial growth in the airways.[15] The inflammatory reaction consists of the production of neutrophil interleukin-8 from epithelial cells, which functions as a secretagogue, which increases mucus secretion, thus creating a positive feedback loop of mucus secretion with persistence of inflammation, infection, and structural damage.[15] The result of this cascade is obstruction of the airways, resulting in lung ventilation failure.[15] Eventually, the damage can become so severe that it becomes life-threatening.[22] The lung function of a person with CF will continue to deteriorate over time, and without proper management, it can lead to death.[22]

In particular, Bronchiectasis is a type of lung disease characterized by the widening and permanent dilation of the bronchial tubes.[22] This condition occurs next to blood vessels in the lungs. In this disease, the combination of airway damage and chronic infection can cause the coughing up of blood, known as hemoptysis, which can vary from small amounts to life-threatening situations.[22]

Accessory Organs - Pancreas, Gallbladder, and Liver:

Pancreatic dysfunction is another common complication of CF, affecting around 80-90% of patients.[23] It is caused by the thickening of secretions in the pancreatic ducts, which occurs when the tiny tubes that transport enzymes out of the pancreas become blocked with mucus, obstructing the normal excretion of pancreatic enzymes and inflammation.[15,24] This can result in malabsorption of fat-soluble vitamins A, D, E, and K, as well as the symptoms of greasy stools, abdominal pain, and malabsorption.[15] Additionally, the reduced pH of the secretions due to the decrease in bicarbonate also leads to the degradation of the enzymes before they reach the intestines.[15] The build-up of enzymes within the pancreas can lead to autodigestion and, ultimately, pancreatitis, an inflammation of the pancreas that occurs in less than 1% of children and 1.6% of adults with CF.[15,23] Sometimes, in severe and chronic cases, endocrine pancreatic failure can occur as a result of damage to the islets of Langerhans, leading to symptoms similar to type 1 diabetes mellitus because the biliary ductules may be plugged with secretions due to the accumulation of mucus.[15] Additionally, obstructive cirrhosis and post-hepatic hyperbilirubinemia can occur.[15] Subsequently, esophageal varices, splenomegaly, and hypersplenism may occur due to increased hepatic portal vein pressures.[15] On the other hand, gallbladder disease is more likely to manifest in CF patients than pancreatic dysfunction, with up to 15% of those with CF having gallstones.[15] However, CF also leads to liver disease, as the blocked biliary ductules in the liver prevent bile from leaving, thus causing inflammation and scarring (fibrosis), resulting in a dysfunctional liver.[25] On top of this, complications such as elevation of serum liver enzymes, hepatic steatosis, focal biliary cirrhosis, multilobular biliary cirrhosis, neonatal cholestasis, cholelithiasis, and cholecystitis can occur.[26]

Intestines:

One of the earliest manifestations of CF, present in 20% of infants with the condition, is meconium ileus.[27] Essentially, CF in the intestines manifests as meconium ileus, the blockade of the intestine by meconium, a newborn's first stool.[15] This is caused by the increased fluid absorption from the malfunctioning CFTR channel, leading to dehydration of the intestinal contents and constipation, in conjunction with the changes inside the intestine due to pancreatic insufficiency.[15]

Reproductive System:

The chronic obstruction of the intestine can lead to inflammation, scarring, and formation of strictures (narrowing of the intestine), which can further be obstructed by fecal impaction or intussusception (telescoping of one part of the intestine into another) later in life.[15] A large majority of men with CF are infertile due to the obstruction or absence of the vas deferens (the tube that connects the testes and prostate gland.)[22] On the contrary, however, it is still possible for the majority of women with CF to become pregnant; they are more likely to experience fertility issues than women without the condition due to a higher risk of ovulation issues from poor nutrition and thicker cervical mucus.[28]

Integumentary System:

The way chloride flows in sweat glands differs from all other tissues that contain CFTR channels.[15] Typically, the chloride channel in sweat glands moves chloride from outside the cells into the cells, which enables the reabsorption of sodium and water back into the body; however, when the CFTR chloride channel doesn't function properly, chloride is not reabsorbed, leading to the loss of sodium and water from the skin surface.[15] This produces the characteristic salty skin seen in CF patients. Moreover, in prolonged warm environments or severe cases, it can cause dehydration due to low sodium levels in the blood.[15]

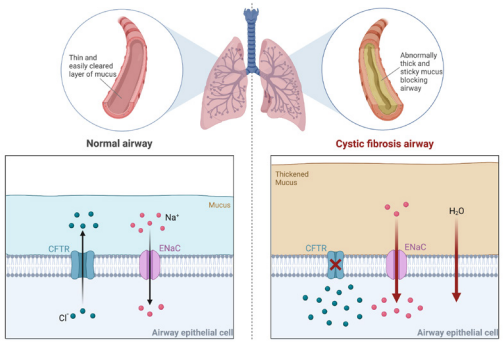

Figure 1: In CF, the production of thick and sticky mucus that clogs the airways leads to recurrent infections. This abnormal mucus buildup can cause

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chronic inflammation, harm to the airways and lung tissue, and a decline in lung function. On the other hand, in a normal airway, the production of thin and clear mucus allows for proper lung function and protection against infections, as it can be easily cleared from the airways.

Pathomechanism:

Although the CFTR protein behaves similarly in different organs, its structure and function vary depending on its location (specific organ). For example, the expression of CFTR may differ in the exocrine glands of different body systems, or it may have different regulatory roles in different organs.[29,30] CF is primarily associated with secretory epithelial cells, such as those found in sweat glands, airways, the pancreas, the gastrointestinal tract, and the vas deferens; however, CFTR channels have also been found in non-epithelial cells, such as those found in blood, the heart, and the brain.[31] According to the Human Protein Atlas, it is mainly expressed in the pancreas and kidneys (Figure 2) and less expressed in the liver, gallbladder, respiratory system, proximal digestive tract, salivary glands, gastrointestinal tract, and the male and female reproductive system.[31] On a cellular level, it has been found in epithelial and endocrine cells and also on the RNA level in immune cells, such as granulocytes and monocytes.[31] CFTR dysfunction affects the secretory functions of organs and regulates many intracellular processes, such as chemokine regulation and glucose metabolism.[31] Additionally, CFTR's location and function may be linked to the plasma membrane and subcellular locations and interference with other intracellular channels.[31]

In a healthy lung and airway cell, the cells that line the epithelium have sodium, chloride, and CFTR channels on their surface, acting as a chloride (Cl-) channel but also regulating other ion channels[32] on airway surface liquid (ASL).[11] Additionally, water follows the Na^{2+} from the ASL into the cells, helping to maintain a healthy airway surface liquid and a healthy airway overall.[11] Conversely, in a cell with a damaged CFTR, chloride transport out of the cell is impaired, leading to an accumulation of chloride ions inside the cell. This increases the electrochemical gradient across the cell membrane, which drives increased sodium transport into the cell by other channels.[33] This excess amount of sodium forces excess water to flow out of the airway surface liquid, leading to volume loss due to water loss and thick, dehydrated mucus.[11] Overall, the CFTR regulates fluid distension and mechanical stimulation of the developing lung, and mutations in CFTR can cause a plethora of other diseases where airway cell CFTR channels are defective or absent.[11,34,35]

Methodology

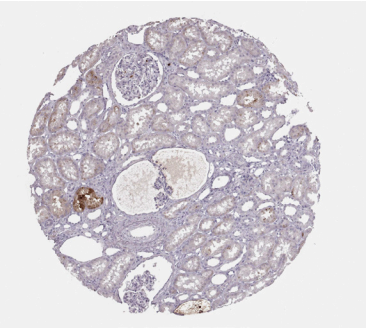

Figure 2: Snapshot from the Human Protein Atlas of the tissue expression of CFTR in the kidneys[36]

Molecular Genetics of CF :

As mentioned in the Pathology of Cystic Fibrosis section, the CFTR codes the CFTR protein, which forms the CFTR channel and encodes 1480 amino acid long channel proteins with a semi-symmetrical structure.[31] It comprises two parts that span the cell membrane, two parts that bind nucleotides within the cell, and one unique regulatory domain.[31] The activity of the CFTR channel can be controlled by phosphorylation, which is a process where enzymes (cAMP-dependent protein kinase A (PKA) and protein kinase C (PKC)) attach a phosphate group to specific sites on the regulatory domain.[31] This changes the protein's attraction to a molecule called ATP, which controls the channel's opening and closing.[31]

Association with Other Proteins:

The CFTR protein is related to other membrane proteins in a regulatory complex, which includes other transport proteins such as the epithelial sodium channel.[37] These proteins all work together to regulate the flow of ions across the cell membrane.[37] Due to this diversity of proteins that interact with CFTR, there are large variations in the severity and symptoms of the disease among patients with similar genetic mutations.[15]

Regulation of CF by Other Proteins:

The CFTR protein comprises several structural domains responsible for its proper folding, stability, regulation of channel opening and closing, selective permeation of chloride ions, and localization and function at the plasma membrane.[38] Normally, it consists of two transmembrane domains (TMD1 and TMD2), two cytosolic nucleotide-binding domains (NBD1 and NBD2), and a regulatory R-domain (Figure 3).[11] The TMD1 is linked to NBD1, and TMD2 is linked to NBD2, forming two TMD-NBD complexes that are united by the R-domain.[30] The TMDs form the ion channel of the CFTR protein, while the NBDs regulate its opening and closing.[30] As the CFTR channel is dependent on ATP, its opening requires phosphorylation of the R-domain by the protein kinase A (PKA) and ATP binding to the NBDs, leading to their dimerization, which allows chloride (Cl-) ions to exit the epithelial cells.[30] The closing of the channel is triggered by the hydrolysis of ATP, which leads to the separation of the NBD dimer and the restoration of the original closed TMD conformation.[30]

In CF, the N-terminus of CFTR binds to the N-terminus of syntaxin 1, a protein that plays a role in the fusion of vesicles at neuronal synapses and in the airway epithelium.[37] This binding between the two proteins interferes with the activity of CFTR channels. It affects the normal functioning of the cell membrane, which can lead to the symptoms associated with CF.[37] The DTRL motif at the C-terminus of CFTR binds to scaffolding/adaptor proteins such as EBP50 (a sodium hydrogen exchange regulatory factor), CFTR-associated ligand, CAP70, and Shank2.[37] To add, phosphorylation of the R domain stimulates CFTR channel activity. It is regulated by protein kinases A and C (PKA and PKC).[37] Overall, these interactions regulate the maturation, oligomeric state, channel gating, and phosphorylation state of the CFTR protein.[37]

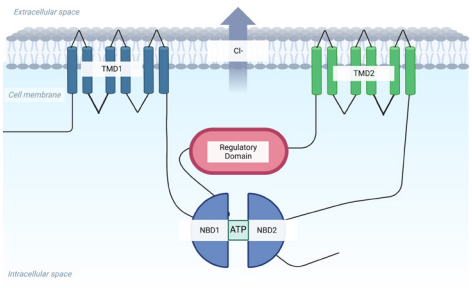

Figure 3: This figure was adapted from "CFTR and Cystic Fibrosis: A Need for Personalized Medicine" by Neil A. Bradbury and "CFTR Protein: Not Just a Chloride Channel?" by Laurence S. Hanssens, Jean Duchateau, and Georges J. Casimir.[30,39] The schematic representation illustrates the normal CFTR, the molecules it interacts with, and the Cl- exiting the apical membrane.

Intracellular Vesicles in CFTR:

CFTR is not only found in the plasma membrane but also in various intracellular compartments, such as endosomes, Golgi, and lysosomes.[31] Within a cell, the protein goes through cycles of being taken into the cell through clathrin-coated vesicles, endosomes, and Golgi and then recycles back to the plasma membrane.[31,40] During this process, intracellular vesicles help with CFTR's transportation.[40]

CFTR also has been shown in alkalizing vesicles, indicating that it may have a role in regulating pH levels within cells.[31] In conjunction with this, long coding RNAs (lncRNAs) also regulate CFTR by controlling its folding at the endoplasmic reticulum and regulating its chloride channel kinetics associated with certain mutation.[41]

Types of CFTR mutations:

Currently, there are over 2,500 identified mutations of the *CFTR* gene that have been identified as causing CF.[11] These mutations can be classified into seven major classes based on their effects on the CFTR protein.[42] The following section will describe each class of mutation (Figure 4).

Class I (protein synthesis defect) in CF mutations include frameshift, splicing, or nonsense mutations that cause the production of an abnormal or truncated CFTR protein, resulting in severely reduced or no CFTR expression.[42] These mutations introduce premature termination codons (PTC), leading to the protein being non-functional.[42] Recently, De Boech and Amaral proposed dividing the traditional class I mutations into classes: Class I and Class VII.[43] Class VII mutations have the same outcome as class I mutations but cannot be rescued by corrective therapy.[43]

Class II mutations (maturation defect) in CF are the most common of the seven and lead to a defect in the folding of the CFTR protein and premature degradation by the endoplasmic reticulum (ER) quality-control system.[42] This impairs the protein biogenesis and reduces the number of CFTR molecules that reach the cell surface.[42] One of the most common instances of a class II error is the codon deletion for a single amino acid (phenylalanine) at the 508 position (ΔF508).[14,45] This mutation is present on at least one allele in approximately 90% of patients with CF in Europe and North America. It impairs protein folding, plasma membrane expression, and the function and stability of CFTR.[35] Specifically, this deletion removes a single amino acid from the CFTR protein, preventing it from staying in the correct 3-D shape.[14]

Class III mutations (gating defects) in CF are full-length CFTR proteins incorporated into the cell membrane but with a defect in its regulation or gating. This leads to no chloride ions flowing through the CFTR channel.[46] This means that the CFTR channel cannot open, as the mutation causes the gate of the channel to be locked in a closed position, which thus prevents the flow of chloride ions across the cell membrane.[14] The most common Class III mutation is G551D, which results from a change of the glycine at position 1784 in exon 11 of the *CFTR* gene to an aspartate.[47] It causes an open channel conformation, which affects the chloride transport.[46]

Class IV mutations (conduction defects) in CF are caused by a change in one of the amino acids of CFTR, which results in the protein forming the correct 3D shape but malfunctioning.[14] These mutations have been shown to decrease the channel's conductance by hindering the ion conduction pore, resulting in lower unitary conductance.[47] However, for CFTR to work correctly, chloride must be able to flow easily through the protein's channel.[14]

Class V mutations (reduced quantity) in CF are characterized by a decrease in the number of functional CFTR channels in the cellular membrane due to the acceleration of their degradation by cellular processes.[15] This is caused by mutations that affect the stability of the mRNA or the mature CFTR protein, leading to a reduction of the concentration of the CFTR channels.[15]

Class VI mutations (reduced stability) in CF affect the stability of the CFTR channel after it has left the endoplasmic reticulum (ER) and at the cell membrane.[42] These mutations reduce the conformational stability of the channel and generate additional internalization signals, causing a faster turnover rate at the cell membrane and reduced expression of the channel at the apical cell membrane.[42]

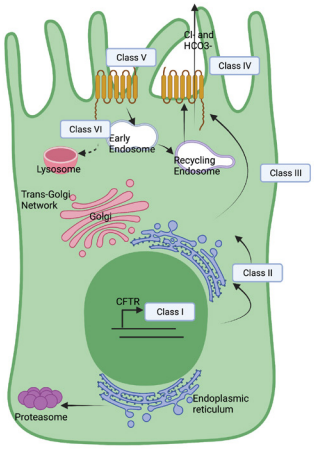

Figure 4: is from "Ion Channels and Transporters as Therapeutic Agents: From Biomolecules to Supramolecular Medicinal Chemistry" by Giacomo Picci, Silvia Marchesan, and Claudia Clatagiro. Class I is a protein synthesis defect, Class II is a maturation defect, Class III is a gating defect, Class IV is a conductance defect, Class V is reduced quantity, Class VI is reduced stability, and Class VII is a CFTR defect.[42,43] Class I–III are more severe, and most of the mutations in Class IV–VI are of a mild form.[44].

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Limitations of the Classification System:

Currently, the treatments using only one drug for certain mutations designated as class I, class II, or class III/IV are ineffective. This may be due to the multiple molecular defects caused by a single mutation.[42] disease severity variation among patients with the same CFTR mutations needs to be better understood.[49] Studies suggest that this variability may be due to differences in expression levels of the mutated gene or other genetic factors.[49] A deeper understanding of these multiple molecular defects caused by a single or a combination of mutations can be beneficial for developing better treatments and drug combinations.[42]

Splice site mutations:

Splice site mutations in the CFTR gene are another common cause of the disease and prevent the cell from correctly interpreting the instructions for creating the CFTR protein, leading to premature termination of the protein production.[14] These mutations are divided into two classes: class I mutations that affect canonical splice sites and class V mutations that create new splice sites.[50] The 3849 + 10 kb C → T mutation, found in 1-2% of individuals with CF, is a common splicing mutation that creates a new donor site 10 kilobases (kb) into intron 19 of the gene.[51]

Emerging Therapies

Therapeutic Agents for Symptomatic Improvement:

Managing CF not only involves addressing the genetic mutation that causes the disease but also treating the symptoms that result from it.[7] The following section will address agents used to reduce inflammation, prevent infections, keep the airways hydrated, and maintain proper nutrition.[7]

To reduce inflammation, there are a wide variety of agents under testing. These include Andecaliximab, which is an antibody to Matrix metalloproteinase 9 (MMP9), POL6014 to block neutrophil elastase function for reducing tissue destruction and lung inflammation, LAU70b, a fenretinide to reduce the inflammatory response in the lungs CTX-4430 to decrease inflammatory mediators, and α-1 antitrypsin, CTX-4430, Elastase Inhibitor AZD9668, JBT-101 (phase 2) for reducing inflammation.[7]

To rehydrate the airways, a wide variety of agents are currently under testing. These include AZD5634 to block the sodium channel in the CF airway to rehydrate and thin the mucus in the lungs, SPX-101 to block sodium channel function in the lungs, ORP-100 to thin mucus in the airway, and bronchitol, which is already approved in the UK.[7]

Modulator Therapies:

Drugs:

There is increasing evidence that the effectiveness of drugs that have been approved or are being tested in the laboratory may vary based on different mutations within the same class.[42] The following section will detail these drugs.

Elexacaftor/Tezacaftor/Ivacaftor (Trikafta®):

Trikafta is a drug combination that combines elexacaftor, tezacaftor, and ivacaftor. It works by using elexacaftor (a corrector) to help the CFTR protein with an F508del mutation fold into a more correct shape, then activating the protein to allow for the increased flow of chloride ions.[14] Although this drug combination is not a complete cure, it helps to alleviate the symptoms of CF by allowing the mutant CFTR protein to move some chloride ions.[14]

Ivacaftor (Kalydeco®):

In 2017, the FDA approved the drug Kalydeco® for treating CF caused by class III mutations.[52] The drug, which contains ivacaftor (a potentiator), works by increasing the activity of the normal CFTR protein present in these patients by binding to the defective protein to keep the channel open for more extended periods of time, allowing more chloride to flow through.[52]

Lumacaftor/Ivacaftor (Orkambi®):

The FDA approved Orkambi for people with two copies of the F508del mutation. It combines lumacaftor (a corrector), which helps the F508del-CFTR protein form the proper shape, traffic to the cell surface, and stay there longer with Ivacaftor.[52] If lumacaftor were to be used alone, only about a third of the CFTR protein would reach the cell surface, and those proteins do not open enough to allow chloride to pass through the cell membrane; thus, the combination of a corrector and a potentiator is most effective, as it would hold the gate open so that enough chloride can flow.[52] Orkambi is approved for people ages one and older with two copies of the F508del mutation.[52]

Tezacaftor/Ivacaftor (Symdeko®):

In 2020, the FDA approved Symdeko, a combination of tezacaftor and ivacaftor, targeting these specific splice mutations.[14] The tezacaftor here acts the same way as lumacaftor in Orkambi, but the Symdeko combination has fewer side effects (e.g., chest tightness) and drug interactions than Orkambi.[52] Symdeko is approved for people ages six and older with two copies of the F508del mutation or if they have 1 out of 154 specified mutations (Figure 4).[52]

The variety of modulator therapies accounts for the different classes of mutations in CF, as each different drug targets a different type of mutation.

Antisense oligonucleotides for CF Splicing Mutations:

Oligonucleotide-based therapies are also being developed to correct mutations in the CFTR gene that cause CF.53 Antisense oligonucleotides (ASOs) have been shown to promote the skipping of specific exons (exon 23) in the CFTR-W1282X mRNA, resulting in a correctly spliced mRNA, thus also resulting in the production of a functional CFTR protein.[53] ASOs have also been used to correct aberrant splicing caused by the CFTR c.2657+5G>A splicing mutation, which is another splicing mutation.[48]

VX-809:

Lastly, VX-809 is an antisense oligonucleotide therapy used to treat CF.[54] It modulates pre-mRNA splicing in a target-specific manner, using short, chemically modified phosphorodiamidate morpholino oligomers (PMOs) to correct the CFTR gene.[54] VX-809 has been shown to be effective in improving CFTR channel function, comparable to that observed with C18 (VX-809 analog) and VX-770 treatment.[54] Moreover, it is also used in combination with other

drugs, such as lumacaftor/ivacaftor combination therapy and exon-skipping antisense oligonucleotides for CF.[55]

Conclusion and Perspective

CF's devastating impacts on the GI tract, respiratory system, and reproductive system have severely deteriorated the quality of everyday life for people with the condition. Not only are patients physically impacted, but all aspects of their lives are as well – from the time-consuming hospital visits they must juggle their personal and professional lives around to the mentally draining treatments they must undergo to manage their symptoms, it is certainly mentally draining. This makes it so much more important to acknowledge the difficulties they face – past the surface level, and by learning about the underlying mechanisms to advance our knowledge, better-targeted treatments can be developed. Depending on the mutation's impact on the chloride ion channel's function, classifications can be made of the mutation type. Thus, based on these classifications, types of medications are made as well. Additionally, a better understanding of the mutations of CF can better equip families with a history of CF for the future since it is a genetic disorder. From this, patients can get a more accurate disease diagnosis sooner. Moreover, learning about the pathomechanism of this autosomal recessive disorder may also aid us in examining the characteristics of other similar disorders on a molecular level in the future.

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