

# [Effect of cystic fibrosis on epithelial cells biology essay](https://assignbuster.com/effect-of-cystic-fibrosis-on-epithelial-cells-biology-essay/)

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) is a glycoprotein found in the plasma membrane of exocrine organ cells, and is composed of about ~1500 amino acids1, 2. Identified as an ion channel, the CFTR is composed of five domains: 2 transmembrane domains, 2 nucleotide-binding domains (NBD) and an R domain1, 5. Transmembrane domains have 6 alpha helixes each, and are embedded in the plasma membrane as a transmembrane protein like its name suggests. NBDs are connected to transmembrane domains, and its role is to interact with ATP for opening of the ion channel, along with the R domain1. R domain, a domain that is unique only to the CFTR protein, regulates the ion channel along with NBDs by ATP phosphorylation1.

CFTR is found in cells of most exocrine organs, including the lung, liver, pancreas, and the sweat glands1, 3, 4. In a normal individual, CFTR protein plays a significant role over reabsorption of salt in some tissues such as the sweat glands, while in other tissues (like the intestines), CFTR regulates hydration of the lumen by secreting Cl- ions1. Protein kinase A phosphoylates the NBDs and the R domain, which then activates CFTR. When NBD and the R domains are phosphoylated by ATP, lung cells then are able to secrete Cl- ions via activated CFTR, and water follows Cl- ions outside the cell due to the hypertonicity of the cell1.

However, this is not the case for patients suffering from Cystic Fibrosis (CF). Cystic Fibrosis is mostly caused by mutations in the CFTR gene3. F508, a common mutation of the CFTR gene, deletes 3 base pairs from the nucleotide sequence of the CFTR gene3. Although the deletion seems miniscule, this mutation alters the phenotype of the CFTR protein, rendering CFTR protein useless. The CFTR protein is still found in patients with F508 mutation, but the protein loses its function, and does not allow passage of Cl- ions3.

Most CF patients with F508 mutation find their condition fatal before the age of 302. In the lung for example, mutated CFTR protein does not allow Cl- ions to escape into the lumen1, 4. This creates a build up of Cl- ions and negative charge inside the cell, which increases the intake of positive Na+ ions via Na+ channels into the cell to balance the negative charge. Due to hypotonicity of the cell because of unbalanced ion levels, the cell increases the intake of water from the lumen. This results in dehydration of the lungs and buildup of thick mucus in absence of water1, 2, 4. The thick mucus layer is harder for cilia on the lung cells to remove, and therefore debris and bacteria from inhalation sticks to the mucus layer. The mucus layer can obstruct the air passages, as well as increase the chance of bacterial lung infection.

Although treating CF has become more effective in recent years, there is still no known cure for CF2. Curing CF would mean restoring CFTR′s function and phenotype in all cells that contain CFTR in their plasma membrane, but this has proven to be a difficult task, because CFTR are found in various types of cells, and its mechanism changes slightly depending on the tissue the protein is embedded in2. A research in gene therapy does not aim to cure CF completely, but rather targets defect CFTR proteins in the lung of the patient by delivering normal CFTR genes to the target tissue, allowing normal CFTR production in epithelial cells of the lung2.

Gene therapy research by Genetic Science Learning Center in University of Utah is looking at inserting a CFTR gene into a vector (eg. a virus), and infecting lung cells with modified viruses which will integrate the normal CFTR gene into the gene of the host cell2. The host cells which are integrated with normal CFTR genes will produce functioning CFTR proteins, removing the effects of dehydration and thick mucus in the lungs. Lung cells were chosen because the modified virus can be easily delivered via inhalers2.

Theoretically, gene therapy seems promising for curing CF, but researchers have faced many challenges. Human trials for gene therapy were run in 1993, 1995, and 1998, and all trials proved ineffective in treating CF in the lungs2. The first human trial in 1993 used adenovirus as a vector, and delivered full length CFTR gene to lung cells using inhalers2. The results showed that because of the low doses of adenovirus in the treatment, the virus could not enter and infect lung cells easily. When patients were treated with higher doses of genetically modified viruses, an immune response was triggered in most patients, and they fought off the adenovirus2. Similar results were shown in human trials of 1995 and 1998.

In conclusion, Cystic Fibrosis is the result of a mutation of the CFTR gene that disrupts the phenotype of the CFTR protein found in the plasma membrane of exocrine organs1-5. Loss of function in CFTR protein does not allow exchange of Cl- ions between the cytoplasm and its environment, which affects Na+ and water concentration of the cell and the lumen. By inserting a normal CFTR gene into cells affected with CF, gene therapy researchers hope to create normally functioning CFTR proteins in the plasma membrane of the cells, but integrating the normal CFTR gene into an affected cell have proven to be a difficult task2.

## Annotated References

1. Hwang, TC, Nagel, G, Nairn, AC, & Gadsby, DC. (1994). Regulation of the gating of cystic fibrosis transmembrane conductanceregulator c1 channels by phosphorylation and atp hydrolysis. Proceedings of the National Academy of Sciences of the United States of America, 91(11), 4698-702.

The article studies the mechanism behind opening CFTR protein to allow exchange of Cl- ions. It goes to explain the structure of CFTR, as well as the molecules/enzymes involved such as protein kinase A.

2. Genetic Science Learning Center (2010) Choosing a vector for CF gene therapy. University of Utah Learn. Genetics. Retrieved February 15, 2010, from http://learn. genetics. utah. edu/content/tech/genetherapy/cysticfibrosis/vector. html

These case studies explain Cystic Fibrosis disorder in depth, and explain why CF is a good candidate for gene therapy. The study also describes how gene therapy can be used to treat CF.

3. Bobadilla, JL, Macek, M, Fine, JP, & Farrell, PM. (2002). Cystic fibrosis: a worldwide analysis of cftr mutations–correlation with incidence data and application to screening.. Hurn Mutat, 19(6), 575-606.

This article looks at mutations that occur frequently on the CFTR gene, and identifies Delta F508 allele as the most common mutated allele.

4. Xu, Y, Szep, S, & Lu, Z. (2009). The Antioxidant role of thiocyanate in the pathogenesis of cystic fibrosis and other inflammation-related diseases. PNAS, 106(48), 20515-20519.

The article describes the cells CFTR protein can be found in. The article also briefly describes the consequences of a thick mucus in the lung, and the mechanism of CFTR.

5. Arcellana-Panlilio, M. (2010, February 02). Plasma membrane ii. Retrieved from https://blackboard. ucalgary. ca/webapps/portal/frameset. jsp? tab\_id= \_2\_1&url=%2fwebapps%2fblackboard%2fexecute%2flauncher%3ftype%3dCourse%26id%3d\_73080\_1%26url%3d

The notes describe the structure of and mechanism of CFTR protein in detail. Notes also describe the importance of tonicity between the cell and its environment.