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Genetics Topic Assignment

Throughout the world, many people are afflicted with various types of genetic diseases. From Huntington's disease to Hemophilia, each disease has its own genetic mutation that affects how the abnormal function of genes and proteins can affect the body as a whole. One example of a genetic disease caused by a genetic mutation is a disease called "Cystic Fibrosis." (CF) Cystic Fibrosis is an autosomal recessive genetic disease where epithelial cells that can be found in the body will produce an abnormally thick mucus that can accumulate in various parts of the body, like the respiratory system.[1] Something like this could cause severe respiratory issues that could effectively "plug-up" the person's airway and heavily affect breathing efficiency. Cystic Fibrosis is a disease where its cause can be very detrimental to people if they are not careful.

Now under normal circumstances, the gene that deals with Cystic Fibrosis is a gene sequence on the 7th chromosome called the "cystic fibrosis transmembrane conductance regulator (CFTR) gene." This gene encodes for proteins that epithelial cells utilize called "cystic fibrosis transmembrane conductance regulators." These proteins normally help the cell by functioning as a channel across the cellular membrane that allows the cell to produce mucus, saliva, tears, digestive enzymes, etc.[1] It does this job by acting as a transport channel for chloride ions to pass into and out of the cell. With this job of transporting chloride ions into and out of the cell, it would allow proper water movement into and out of the cells/tissues as well. This proper movement of water is necessary to help with the production of thin mucus that the cell can then secrete into various parts of the body like the lining of the digestive system, respiratory system, reproductive system, and various other organs and tissues around the body. However, chloride ions are not the only types of ions it allows to transport. The CFTR protein also assists in the transport of sodium ions across the cellular membrane as well. This additional sodium ion transport also helps in allowing proper water movement in and out of the cells. When these normal functions of the CFTR protein are carried out, epithelial cells and other cells that secrete mucus can properly secrete thin mucus in order to fulfill the job of providing the body with mucus to lubricate the organs and bodily passages.

However, whenever there is a mutation on the CFTR gene, this can result in Cystic Fibrosis to develop. As of right now there are five different ways for a mutated CFTR gene to develop into full-blown CF. Firstly, the mutated CFTR gene allows for improper production of the CFTR proteins. Secondly, the mutated CFTR gene allows for improper processing of the CFTR proteins. Thirdly, the mutated CFTR gene allows for improper gating of the CFTR proteins. Fourthly, the mutated CFTR gene allows for improper amino acid conduction in each CFTR protein. Lastly, the mutated CFTR gene allows for an overall reduction in the number of CFTR proteins that are present in the cellular membrane at a given time. Each of these different classes of mutations can result in Cystic Fibrosis but each class has a different pathophysiological effect on the CFTR protein and its ability to function properly.

The first class of Cystic Fibrosis involves the mutation of the CFTR gene that results in the improper production of the CFTR protein. This means that there are some nonsense and splice mutations that ultimately affect the production of the CFTR protein. It does this by having a nonsense gene mutation that gets carried over to the mRNA strand that codes for the protein. While the mRNA was being transcripted, since there was a nonsense gene mutation on the DNA strand, there was an early stop signal encoded on the mRNA strand as well. This early stop signal could lead to the premature ending of the production of the CFTR protein. Therefore, the process of translation would continue until it reads the premature termination codon and stops the full completion of the protein. When this occurs, since the process was interrupted, no function CFTR proteins are made properly to be embedded in the cellular membrane to then do its job of proper sodium and chloride transport.

The second class of Cystic Fibrosis occurs when the mutation of the CFTR gene results in the removal of a single amino acid in the polypeptide that makes up the CFTR protein. This occurs when some nucleotides are removed so that when the mRNA strand is made, the codons it contains would make-up the removal of an amino acid or two. When this occurs, the protein shape that results from this altered polypeptide chain would be abnormal and would prevent normal function of the protein. This would then result in no CFTR proteins being usable for the transport of chloride and sodium in the cell membrane, and lead to the development of CF symptoms to occur.

The third class of Cystic Fibrosis involves the mutation of the CFTR gene that results in a very similar mutation that resembles the second-class mutation.[2] Specifically, this mutation results in the protein channel not being able to open or close to allow the transport of the chloride and sodium ions. This could happen by having an abnormal protein structure due to a missing amino acid or an incorrect amino acid, that affects the final structure of the CFTR protein. This alteration in the protein shape results in the CFTR protein always remaining closed, thereby preventing the transportation of ions across the cell membrane. Now unlike the other mutations, this one can be controlled with drugs like Kalydeco (ivacaftor) that will help by forcing the CFTR channel

proteins open, to reestablish the transportation of chloride and sodium ions, thereby also reducing the symptoms of Cystic Fibrosis.

The fourth class of Cystic Fibrosis involves the mutation of the CFTR gene that results in another similar mutation that resembles the second-class mutation. More specifically, this mutation results in the CFTR protein not being able to transport ions across the membrane, due to the difference in conduction charges of the internal protein environment. This occurs when there is an abnormal internal protein structure, due to the placement of an incorrect amino acid or the missing on an entire amino acid. When this occurs, this change in the proper amino acid sequence will allow the polypeptide chain to fold in an abnormal way where the resulting CFTR protein will have an abnormal internal environment for ions. This would then prevent/slow the transport of ions like chloride and sodium, which would then result in the restricted movement of water into the cells, and lead to further production of thick mucus to be secreted by the cells.

Lastly, the fifth class of Cystic Fibrosis is unique from all the others. It occurs when the mutation on the CFTR gene results in the abnormal number of CFTR proteins in the cell membrane. This could occur for a variety of reasons like too many CFTR proteins not being usable, too many degrading rapidly, etc. Either way it highly resembles the mutations found in the first and second classes of CF. This means that for this class of CF, the mutation on the DNA could either be a nonsense mutation or a mutation that results in abnormal amino acid sequence. Either way the shape of the resulting protein will be abnormal and affect either its function or its stability in the cell membrane, and thereby affect how it properly transports ions into and/or out of the cell. This class of CF can have a serious impact because with the reduced number of proteins for varying reasons, the effects of this type of CF can even affect multiple systems at the same time.

In conclusion, Cystic Fibrosis is an autosomal recessive genetic disease that can affect many people around the world for a variety of reasons. Under normal circumstances, the CFTR protein is supposed to allow proper transport of chloride and sodium ions across the cell membrane. However, there are five different classes of CFTR mutations that can occur. Firstly, there are nonsense mutations on the CFTR gene that allow for the improper production of the CFTR proteins. Secondly, there are missense mutations in the CFTR gene that allow for the improper processing of the CFTR proteins. Thirdly, the mutated CFTR gene allows for improper gating due to an abnormal protein shape. Fourthly, the mutated CFTR gene allows for improper internal protein conduction in each CFTR protein. Lastly, the mutations found in the first and second class could result in the reduction of the number of CFTR proteins that are present in the cellular membrane at a given time. All these classes represent different causes of the same disease that can still have the same devastating effects. In the future, hopefully there will be some type of cure for this genetic disease.

References

1. Declercq, M. et al. The role of endothelial cells in cystic fibrosis. J Cyst Fibros. 6, 752-761. (2019) DOI: 10.1016/j.jcf.2019.07.005

2. Cutting, G. R. Cystic fibrosis genetics: from molecular understanding to clinical application. Nature Reviews Genetics. 1, 45-56. (2015) doi: 10.1038/nrg3849

Genetics Topic Assignment Outline

Topic – Genetics of Cystic Fibrosis, Normal functions of protein encoded, and the various mutations that occur/how it works in an abnormal sense.

- Introduction
- Discuss Cystic Fibrosis, its prevalence, its transmission. End with topic sentence
    - Talk about what Cystic Fibrosis is, genetically.
    - What genes are related to this condition?
- Physiology of normal conditions, what the gene normally functions
- Pathophysiology of mutations, what do they cause?
- Conclusion