CYSTIC FIBROSIS

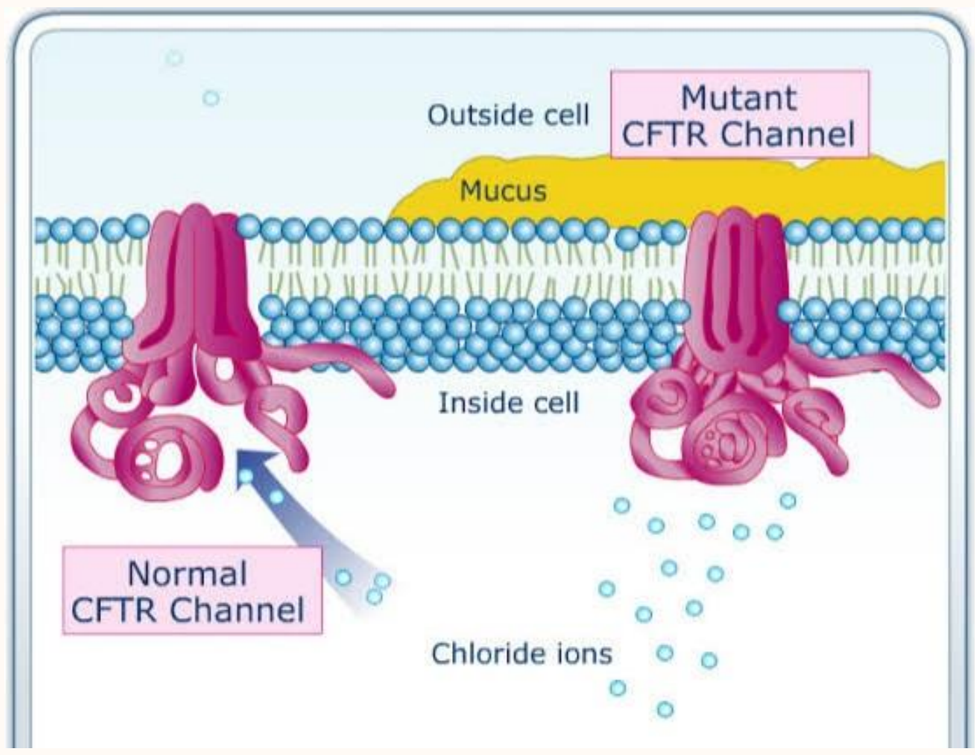
UNDERSTANDING CFTR FUNCTION AND DYSFUNCTION

Background

- A genetic (hereditary) disorder to do with the genetic code of the gene CFTR.
- The CFTR channels chloride ions through epithelial cells to attract water molecules and make mucus less viscous
- Therefore, once cells are unable to bring out chloride ions out of their membrane (to attract water molecules) the mucus cannot be thinned out by the water and so the mucus becomes sticky and thick to the point where it can block airways, making it difficult to perform gas exchange in the lungs.

Molecular Physiology

- The CFTR gene can be located in the long arm of Chromosome-7
- The mutation in a CFTR gene seen in cystic fibrosis is the F508del mutation, the deletion of phenylalanine in the CFTR gene, essentially it means that there is a loss of 3 nucleotides that code for phenylalanine in the amino acid position 508.
- What occurs if the mutated gene is synthesized is that the CFTR protein will be defective in transporting chloride ions in and out of the epithelial cells.
- The reason for its defective ability or disappearance is that the deletion of phenylalanine in the CFTR allows the CFTR gene to go through an impaired post translational modification and the channel protein will not be properly folded. Since the mutated CFTR protein is misfolded, the misfolded protein will reside in the endoplasmic reticulum until it gets degraded.



CFTR Structure

- The CFTR protein is a multiplex protein with 3 domains in the structure of the protein.
- There are nucleotide binding domains attached to each other with a transmembrane protein attached at the top, creating a barrel-like structure that allows chloride ions to easily pass in and out of.
- Another part of the structure is the regulator domain which is attached to the barrel-like structure, and it is usually phosphorylated to be activated and allow the chloride ions to be passed through the channel.
- In the case that it is not activated (phosphorylation does not occur with the regulator domain), the transmembrane channel will be constricted and the chloride ions will be unable to pass through the channel.

Disease Pathology

- Symptoms of Cystic Fibrosis patients can include:
  - Poor weight/height growth
  - Chronic respiratory difficulties
  - Difficulty breathing
  - Chronic constipation/diarrhea
- Since water molecules will not be attracted to the cell membranes, the mucus will begin to build up and cause extensive damage
- This would result in patients having to take daily medication for symptomatic treatment, in replacement for bodily functions that have been blocked by the mucus.

Therapy

- Orkambi
- Symdeko
- Oral Pancreatic Enzymes
- Trikafta
- Antibiotics for lung infections
- Mucus-thinning drugs (hypertonic saline)
- Inhalers