CYSTIC FIBROSIS

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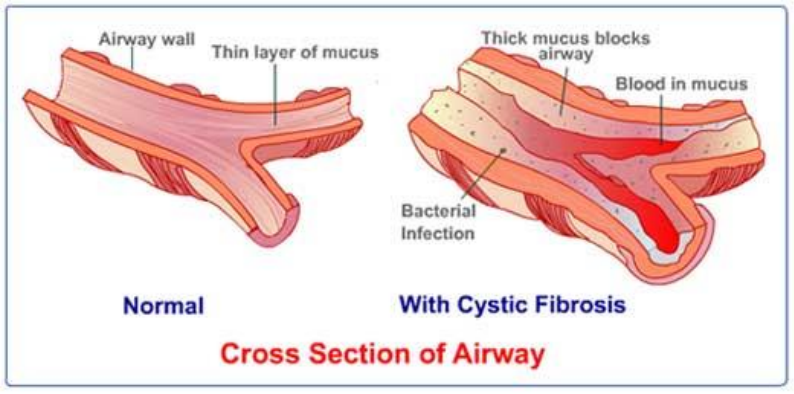
Physiology

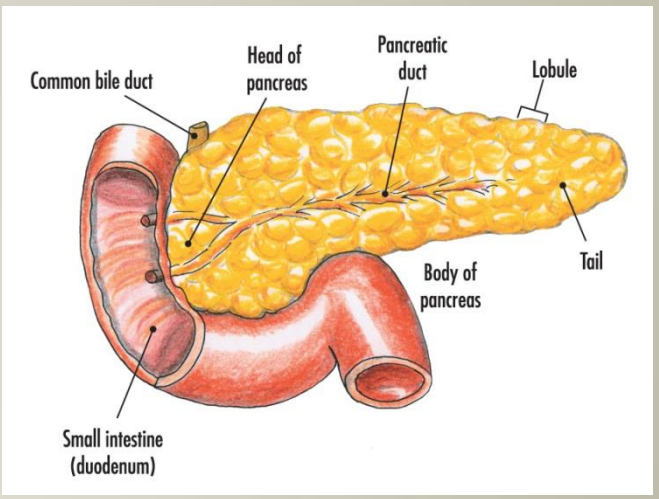
- Cystic fibrosis is the most common autosomal recessive disease, occurring in about 1 in every 3,500 Caucasians, 1 in 17,000 African Americans, and 1 in 31,000 Asian Americans

Fig 1



- Respiratory system:
  - Thick mucus in lungs causes wheezing/coughing
  - Vulnerability to bacterial infection
  - Lowered oxygen intake
- Digestive system:
  - Blockage of pancreatic ducts leads to difficult digestion/absorbtion of nutrients
  - Pancreatitis, esophagitis, cirrhosis of liver, and CF-related diabetes are just some of the complications which can occur
- Reproductive system:
  - Congenital bilateral absence of vas deferens
- Endocrine system:
  - Inability to reabsorb salt during perspiration

Fig 2



Molecular Cause

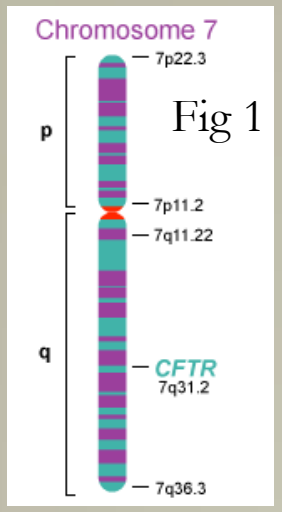


Fig 1

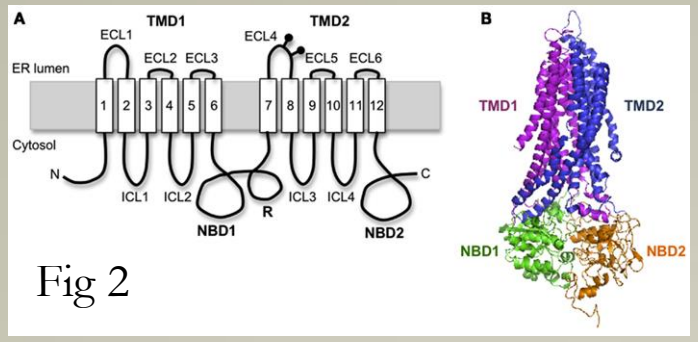


Fig 2

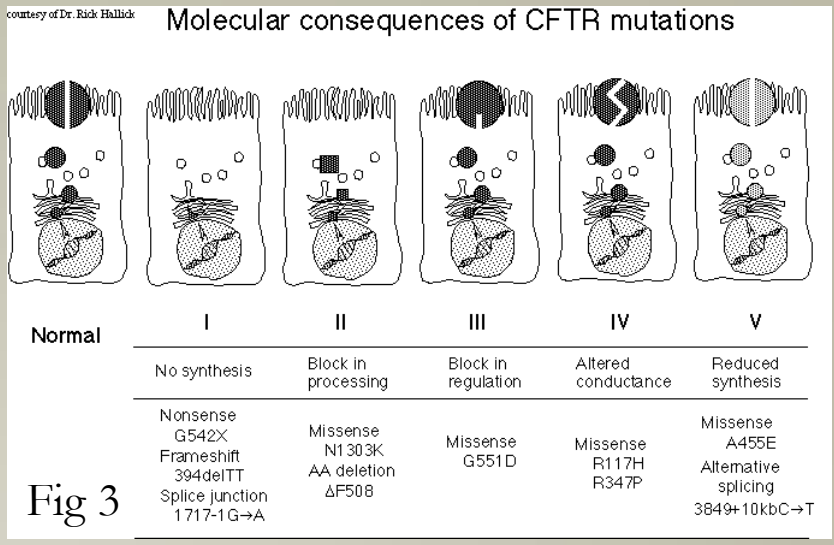
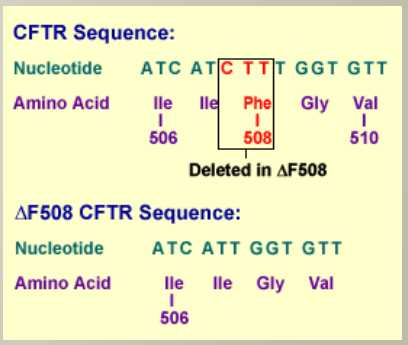


Fig 3

- Autosomal recessive – must have two copies of faulty gene
- More than 900 mutations known, 5 different classes
- Mutations can affect the quantity (due to defective processing/trafficking) or function (affecting the gating/conductance of chloride ions) of the CFTR gene at the plasma membrane
- Most common mutation is a deletion of phenylalanine at position 508 (ΔF508), and the most severe symptoms arise from homozygous ΔF508. This mutation is the cause of about 70% of cases of cystic fibrosis.
- Known as an ATP-binding cassette (ABC) transporter
- CFTR regulates epithelial sodium channels, abbreviated as ENaC, which work together to regulate the passage of chloride and sodium ions (Cl- and Na+). This maintains that balance of salt, fluid, and pH in epithelial tissue. When there is an imbalance, mucus from epithelial tissue becomes thick and sticky instead of free-flowing. Cilia lining the surfaces of the tissues, whose purposes are to help the mucus flow in the right direction, can't beat under the thick mucus, which then builds up in areas like the lungs and pancreas.

Fig 4



Treatment/Risks and Limits

Fig 1

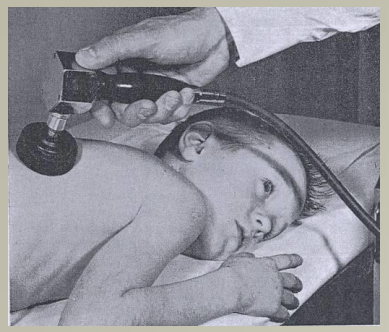


Fig 2

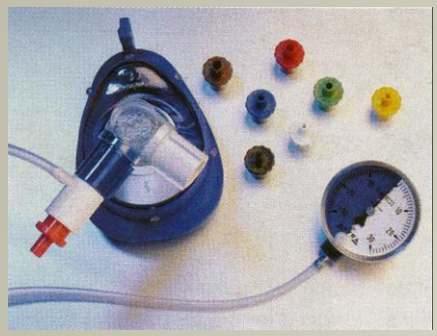
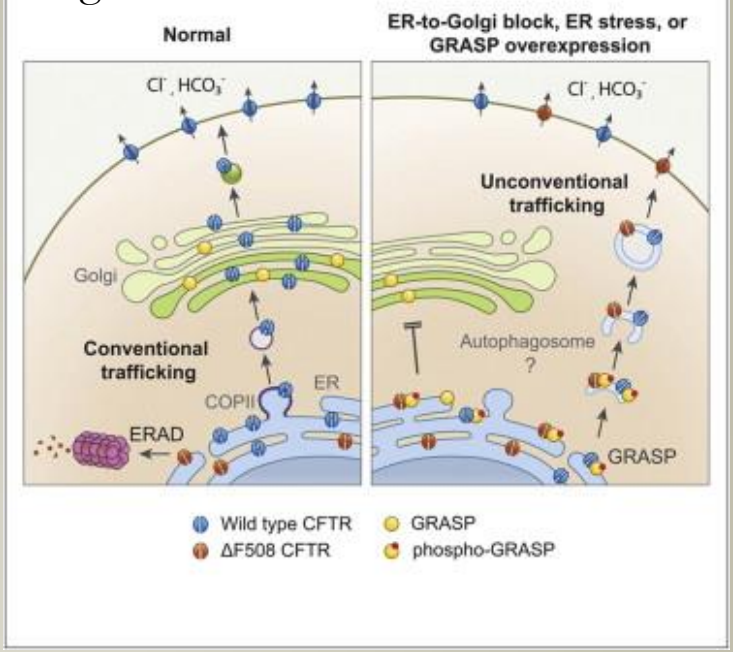


Fig 3

- Current Methods:
  - Anti-inflammatory and mucus thinning medications
  - Physical/breathing exercises and assisting devices
  - Organ transplants or removal
  - Kalydeco, also known as ivacaftor or VX-770. This drug helps improve the function of CFTR with a G551D mutation and is approved for children ages 6 and older. This mutation occurs in about 4% of the CF population (in the U.S.). Current trials are being held with younger children and patients with other mutations.
- Under Trial:
  - Ataluren, also known as PTC123, is a drug which aims to fix premature stops in production of CFTR, such as in the W1282X mutation which is the second most common mutation of CFTR.
  - N6022 is a drug early in trial that increases levels of a signalling molecule called S-nitrosoglutathione (GSNO) which has been shown to increase the amount of CFTR that reaches the membrane
  - VX-661 and VX-809 are compounds designed to move damaged CFTR to the membrane and improve its function, to be used in conjunction with Kalydeco for the ΔF508 mutation
  - Inhalation of molecules of DNA with a functioning copy of CFTR wrapped in a fat globule, which can be absorbed and integrated into the cell
- Limitations:
  - No current treatment for the most common cause of CFTR, ΔF508
  - Medications only treat the symptoms
  - Exercises can be time-consuming/require the assistance of another person
  - Patients can die while waiting for a transplant

Cure Proposal

Fig 1



- In the normal molecular pathway, ΔF508 CFTR is found to be defective by the endoplasmic reticulum due to misfolding, and is ejected to be destroyed by endoplasmic reticulum associated protein degradation (ERAD). Wild type CFTR is fully glycosylated and sent on to the golgi bodies to be transported to the plasma membrane.
- Glycosylation is a post-translational modification. Glycans serve a variety of structural and functional roles in membrane and secreted proteins. The majority of proteins synthesized in the rough ER undergo glycosylation.
- Molecules known as golgi reassembly stacking proteins (GRASPS) may hold the answer to the transport of defective CFTR.
- GRASP homologs in drosophila transport α-integrin, a transmembrane protein, to the membrane via a golgi-independent route.
- The premature, non-fully-glycosylated form of CFTR was found to function as a chloride channel when brought to the membrane.
- Blockage of ER-to-Golgi trafficking would be necessary in order for this approach to work, otherwise GRASP55 would not interact with CFTR.
- This would require a mutant component of anterograde coat protein complex II (COPII), a protein which mediates ER-to-Golgi trafficking. A mutated dominant-negative Sar1 achieved this blockade.
- This technique has been shown to work in mice, *mus musculus*, in vitro and in vivo.
- Limits in humans are so far unknown, as there have not been clinical human trials. The most important step to this cure is actually funding and testing it in humans, and developing a system of distribution if it is successful.

References

- Title Page
  - http://www.clker.com/cliparts/f/c/5/c/12387030674401760 98johnny_automatic_lungs.svg.hi.png
- Physiology
  - Fig 1: http://www.medindia.net/patients/patientinfo/images/cystic-fibrosis-c-s-airway.jpg
  - Fig 2: http://www.londonbridgehospital.com/userfiles/pancreas-text.jpg
  - http://www.nhlbi.nih.gov/health/health-topics/topics/cf/signs.html
  - http://ghr.nlm.nih.gov/condition/congenital-bilateral-absence-of-the-vas-deferens
  - http://www.stanford.edu/class/psych121/humangenome-CF.htm
- Molecular Cause
  - Fig 1: http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/Gifs/chrom7.gif
  - Fig 2: http://c431376.r76.cf2.rackcdn.com/36394/fphar-03-00201-HTML/image_m/fphar-03-00201-g001.jpg
  - Fig 3: http://3.bp.blogspot.com/-dxSvb49hqV8/Tyg3yRAvIyI/AAAAAAAAL10/3sh8hNAo9EE/s1600/CFTR%2BMutations.gif
  - Fig 4: http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/Gifs/CFTRdel4.gif
  - http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/cftr.shtml
  - https://www.cftrscience.com/a_guide.php
- Treatment/Risks and Limits
  - Fig 1: http://www.cfmedicine.com/history/images/Sixties/10Percussor.jpg
  - Fig 2: http://www.cfathess.gr/images/pepmask.JPG
  - Fig 3: http://mms.businesswire.com/bwapps/mediaserver/ViewMedia?mgid=309736&vid=4
  - http://www.cff.org/treatments/Therapies/Kalydeco/
  - http://www.cff.org/research/DrugDevelopmentPipeline/
  - http://hospitals.unm.edu/cf/cf_treatment.shtml
  - http://www.aetna.com/cpb/medical/data/1_99/0067.html
  - http://www3.imperial.ac.uk/newsandeventspggrp/imperialcollege/newssummary/news_16-3-2012-9-48-36
- Cure Proposal
  - Fig 1: http://ars.els-cdn.com/content/image/1-s2.0-S0092867411008191-fx1.jpg
  - http://www.sciencedirect.com/science/article/pii/S0092867411008191
  - http://en.wikipedia.org/wiki/Glycosylation