CYSTIC FIBROSIS (MUCOVISCIDOSIS)

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Cystic Fibrosis

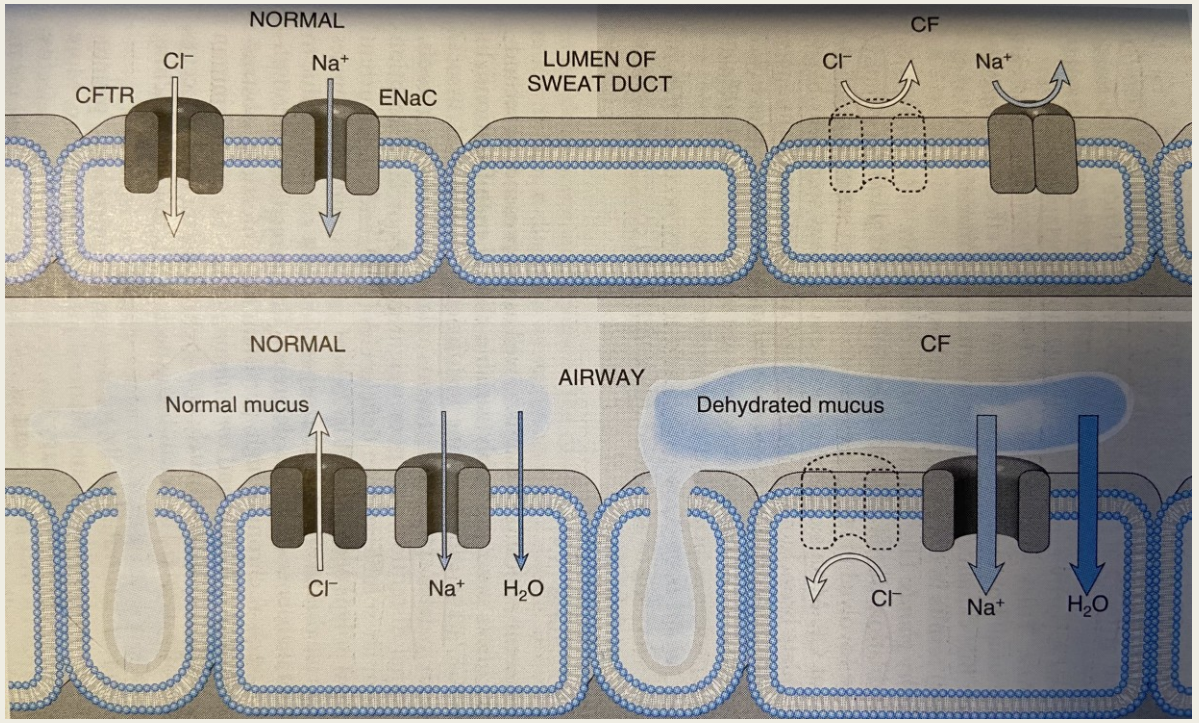
- An AR disorder that affects **epithelial cell ion transport** and causes **abnormal fluid secretion** in **exocrine glands**, as well as in **respiratory, gastrointestinal, and reproductive mucosa**.
- 1 of 2500 live births in US
- The most common lethal genetic disease affecting Caucasian population
- Heterozygote carriers also have a higher incidence of respiratory and pancreatic pathology relative to general population

Cystic fibrosis transmembrane conductance regulator (CFTR) protein

- The gene mutated in CF encodes CFTR protein – a **chloride channe**l; activated via agonist-induced increases in intracellular cAMP, followed by PKA activation and CFTR phosphorylation
- CFTR regulates other ion channels and cellular processes; CFTR association with the **epithelium sodium channel (ENaC)** has the most pathophysiologic relevance to CF (see next page)
- CFTR mediates **bicarbonate transport**. Alkaline fluid (containing bicarbonate) are secreted in normal tissues; in some CFTR mutations acidic fluids are secreted → acid environment → **mucin precipitation & duct obstruction**

CFTR protein

- Tissue-specific CFTR functions
- In *eccrine sweat duct epithelium*, normal CFTR <u>augments</u> ENaC activity. In CF, ENaC activity <u>lost</u> → **hypertonic sweat** (sweat chloride test used for clinical dg.)



- In *respiratory and intestinal epithelium*, normal CFTR <u>inhibits</u> ENaC activity. In CF, ENaC activity <u>augmented</u> → increased sodium movement into the cell → increased osmotic water resorption from the lumen → dehydration of mucus secretions → **defective mocociliary action & accumulation of hyperconcentrated, viscous secretions → obstruct ductal outflow** from the organs

CFTR protein

- At least 1800 disease-causing mutations of CFTR have been identified
- The most common (70% worldwide) is a three-nucleotide deletion coding for phenylalanine at position 508 (delta F508) → **defective intracellular CFTR processing with degradation before reaching the cell surface**
- *Classic CF*: homozygous for delta F508 mutation (or a combination of any two severe mutations) → virtual absence of CFTR function → severe clinical disease incl. early pancreatic insufficiency and various degrees of pulmonary damage
- *Atypical* or *variant CF:* other combinations

Modifiers

- Genetic and environmental modifiers impact CF severity
- Mannose-binding lectin2 (involved in microbial opsonization): reduced expression → increased risk of end-stage lung disease
- TGF-β (a direct inhibitor of CFTR function): polymorphisms exacerbate the pulmonary phenotype
- The nature of secondary pulmonary infection will impact subsequent inflammation and lung destruction

Morphology

- *Pacreas*: 85-90% of patients, ranging from mucus accumulation in small ducts with mild **dilation** to total **atrophy** of the exocrine pancreas. Absence of exocrine secretions → impairs fat absorption → avitaminosis A → ductal squamous **metaplasia**
- *Intestine*: thick viscous plugs of mucus (**meconium ileus**) → small bowel obstruction (5-10% of affected infants)
- *Liver*: bile canalicular plugging by mucinous material → diffuse pancreatic cirrhosis

Morphology

- *Salivary glands*: like pancreas, duct **dilation**, ductal squamous **metaplasia**, and glandular **atrophy**
- *Lungs*: involved in most cases and the most serious complication of CF. **Mucus cell hyperplasia and viscous secretions block and dilate bronchioles.** Superimposed infections and pulmonary abscesses are common. Eg. *S. aureus*, *H. influenzae* and *P. aeruginosa*; *Burkholderia cepacia* is associated with fulminant illness
- *Male genital tract*: **Azoospermia** and **infertility** occur in 95% of male surviving to adulthood, frequently with **congenital absence of the vas deferens**

Clinical features

- In classic CF, pancreatic exocrine insufficiency → **malabsorption**
- → large, foul-smelling stools, abdominal distention and poor weight gain
- → fat-soluble vitamin deficiencies (A,D and K)
- Recurrent sinonasal polyps (10-25%)
- Male **infertility** due to obstructive azoospermia (most commonly due to congenital absence of the vas deferens)
- **Cardiorespiratory complications** such as cor pulmonale are the most common causes of death (approx. 80%)
- Chronic liver disease in 15%
- The mean life expectancy is approaching **40 years**

Treatment

- Traditionally focused on antimicrobials, pancreatic enzyme replacement, and bilateral lung transplantation
- More recently, “potentiator” therapy has been introduced for defective forms of CFTR that are present at normal levels in the cell membrane; partially restore normal ion transport function

Thank you!