Respiratory distress syndrome (RDS)

α1-Antitrypsin (α1- antiproteinase) deficiency

Cystic fibrosis

By

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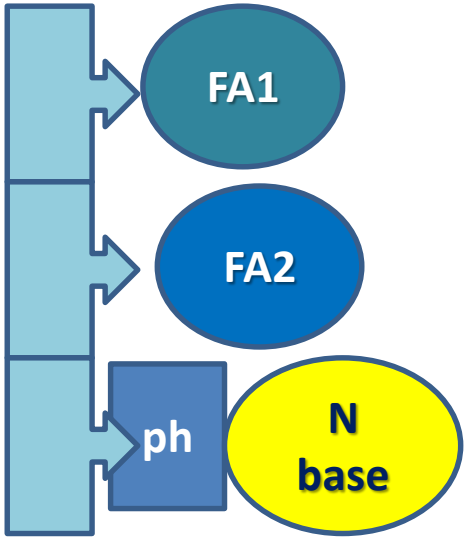
Phospholipids



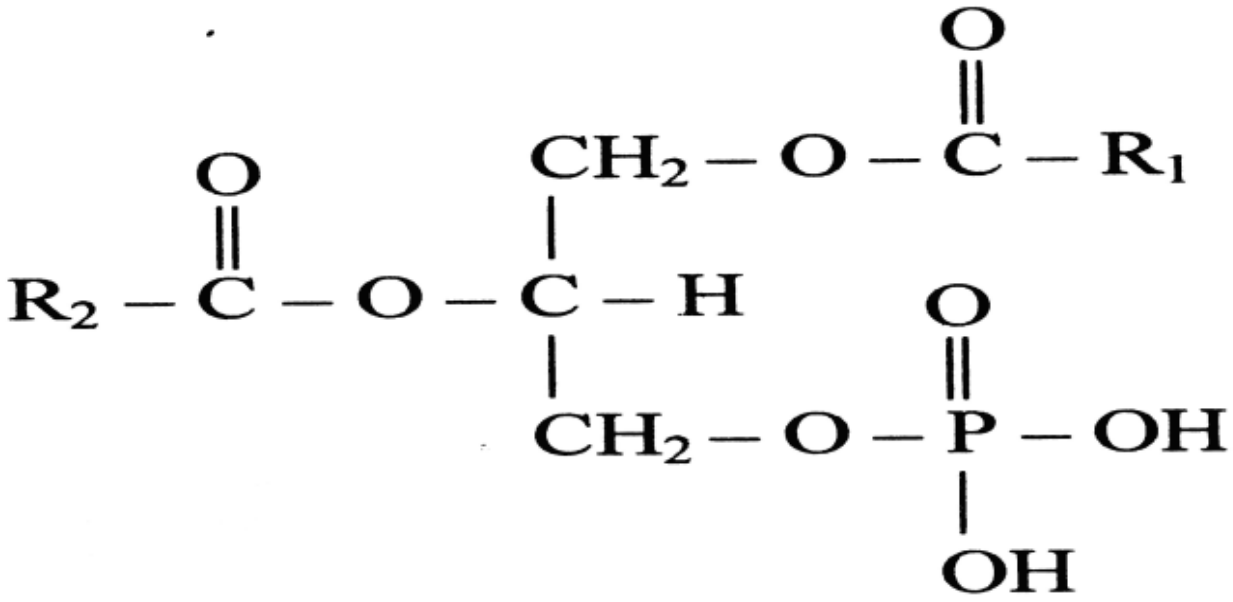
Alcohol + FA (s) + phosphate + base

If the alcohol is glycerol ⟶ Glycerophospholipids = phosphoglycerides

If the alcohol is sphingosine ⟶ Sphingomylines

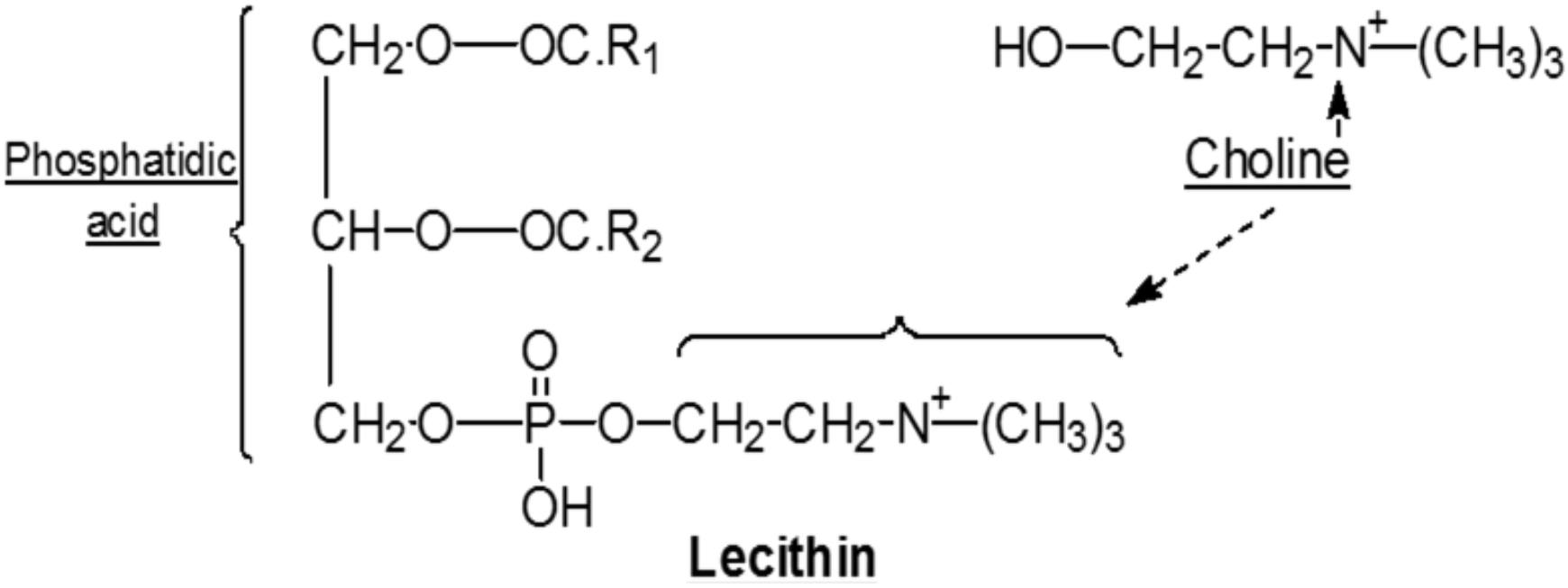
Phosphatidic acid:

- This is the simplest phosphoglyceride, and is the precursor of the other members of this group.



Phosphatidylcholine (lecithin):

- The phosphate group of phosphatidic acid was esterified with choline



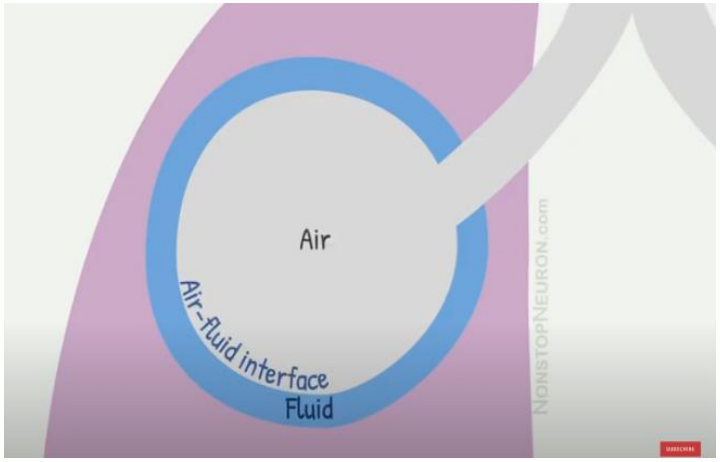
Lecithin

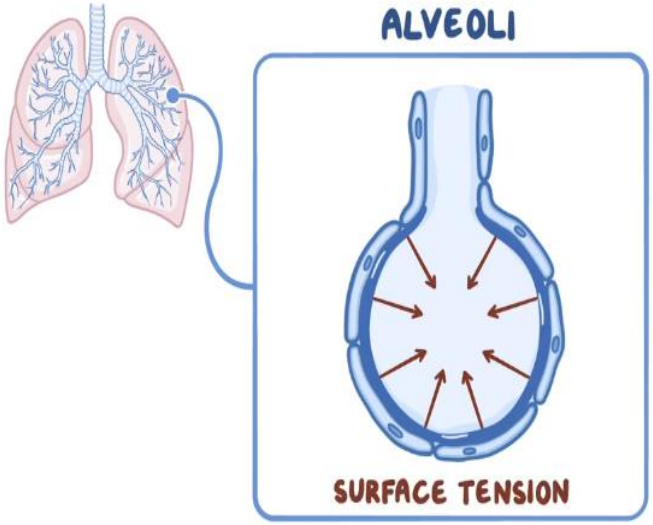
Dipalmitoyl-phosphatidylcholine (DPPC or dipalmitoylecithin)

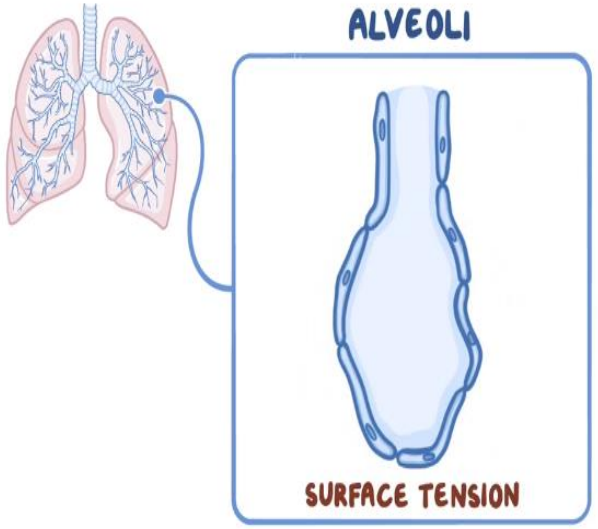
- In DPPC, positions 1 and 2 on the glycerol are occupied by **palmitate**.
- DPPC, made and secreted by granular pneumocytes(Type II pneumocytes), is the major lipid component of lung surfactant (the extracellular layer lining the alveoli).
- Lung surfactant is composed mainly of lipid with some proteins and carbohydrate. Surfactant activity is largely attributed to DPPC , which is synthesized shortly before parturition in full-term infants.

- Surfactant serves to decrease the surface tension of this fluid layer, reducing the pressure needed to reinflate alveoli, thereby preventing alveolar collapse (atelectasis).

- **Respiratory distress syndrome (RDS)** in pre-term infants is associated with insufficient surfactant production, and is a significant cause of neonatal deaths in western countries.


Air
Air-fluid interface
Fluid
NONSTOPNEURON.com


ALVEOLI
SURFACE TENSION


ALVEOLI
SURFACE TENSION

- **Note** : Lung maturity of the fetus can be gauged by determining the ratio of DPPC to sphingomyelin , usually written as **L(lecithin)/S ratio**, in amniotic fluid. A ratio of 2 or above is evidence of maturity, because it reflects the major shift from sphingomyelin to DPPC synthesis that occcurs in the pneumocytes (alveolar cells) at about 32 weeks of gestation.

- Lung maturation can be accelerated by giving the mother glucocorticoids shortly before delivery.
- Administration of natural or synthetic surfactant (by intratracheal instillation) is also used in prevention and treatment of infants RDS.
- Respiratory distress syndrome due to an insufficient amount of surfactant can also occur in adults whose surfactant-producing pneumocytes have been damaged or destroyed, for example, as an adverse side effect of immunosuppressive medication or chemotherapeutic drug use.

α_1-Antitrypsin (α_1- antiproteinase)

- It is the chief **α_1 _ globulin.**
- **Increases during inflammations and in malignancy, and hence the name acute phase proteins or acute phase reactants.**
- **α_1- antiproteinase, is produced by the hepatocytes and macrophages. It forms complexes with plasma serine proteases (trypsin and elastase), inhibiting their activity.**

- When lung infection occurs, the lungs become infiltrated with polymorphonuclear leukocytes to combat infection.
- These leukocytes secrete elastase enzyme to help clear products of infection; excess elastase activity is checked by **α_1-antiproteinase.** **Thus, deficiency of this protein causes damage to lung tissue, leading to emphysema.**
- Smoking inactivates α1- antiproteinase, which explains the occurance of emphysema in smokers.

Cystic fibrosis

- It is an inherited autosomal recessive disorder
- Characterized by:

- Chronic bacterial infections of the airways and sinuses,
- Fat maldigestion due to pancreatic exocrine insufficiency,
- Infertility in males due to abnormal development of the vas deferens,
- Elevated levels of chloride in sweat (>60mmol /L).

- The cystic fibrosis gene known as CFTR occurs on chromosome 7 and encode a protein of 1480 amino acids, named cystic fibrosis transmembrane regulator (CFTR), a cyclic AMP-regulated **CL^- channel.**
- An abnormality of membrane CL^- permeability is believed to result in the **increased viscosity of many bodily secretions.**
- CFTR is involved in production of sweat, digestive fluids, and mucus. When CFTR is not functional, secretions which are usually thin instead become thick

- The commonest mutation in the CFTR gene is deletion of three bases, resulting in loss of residue 508, a phenylalanine so the mutant allele is three bases shorter than the normal allele , it is possible to distinguish them from each other by the size of the PCR products obtained by amplifying that portion of the DNA.
- *The name 'cystic fibrosis' refers to the characteristic fibrosis and cysts that form within the pancreas.*

- The most serious and life threatening complication is **recurrent pulmonary infections** due to overgrowth of various pathogens in the viscous secretions of the respiratory tract.
- The most current theory suggests that defective ion transport leads to dehydration in the airway epithelia, thickening mucus.
- In airway epithelial cells, the cilia exist in between the cell's apical surface and mucus in a layer known as airway surface liquid (ASL).

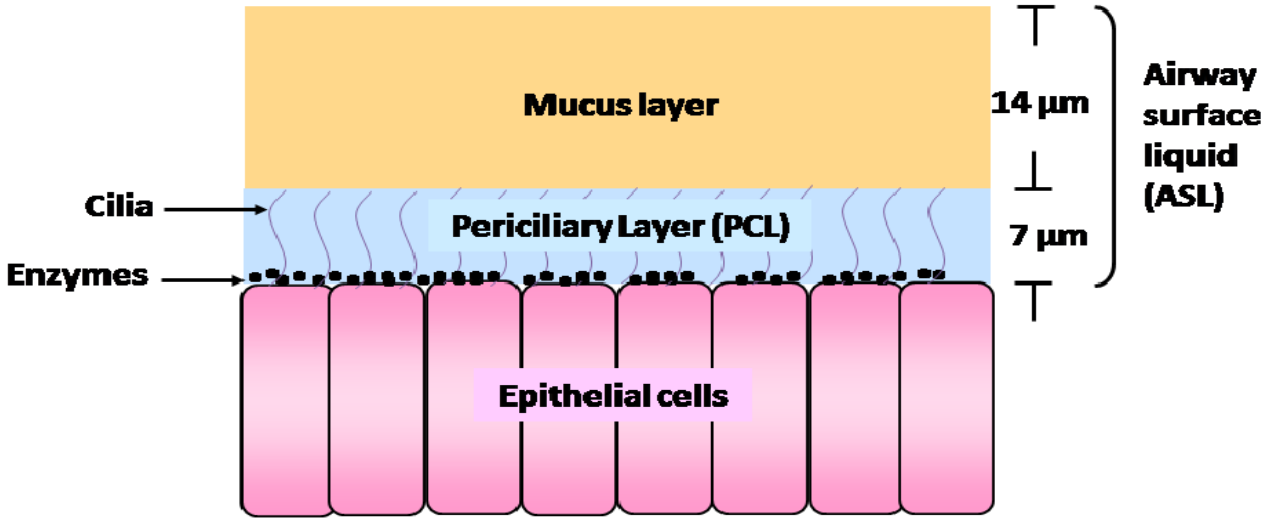


Figure 11: Layer structure of airway surface fluid (ASL) in human lungs. ASL is composed of two major layers: the mucus layer and the periciliary layer (PCL). PCL has similar thickness as cilia, which is about 7 micron. Mucus layer is approximately twice as thick as PCL.

The airway surface liquid consists of a layer termed the periciliary liquid layer and an overlying gel layer termed the mucus layer. The periciliary liquid layer is so named as it surrounds the cilia and lies on top of the surface epithelium.

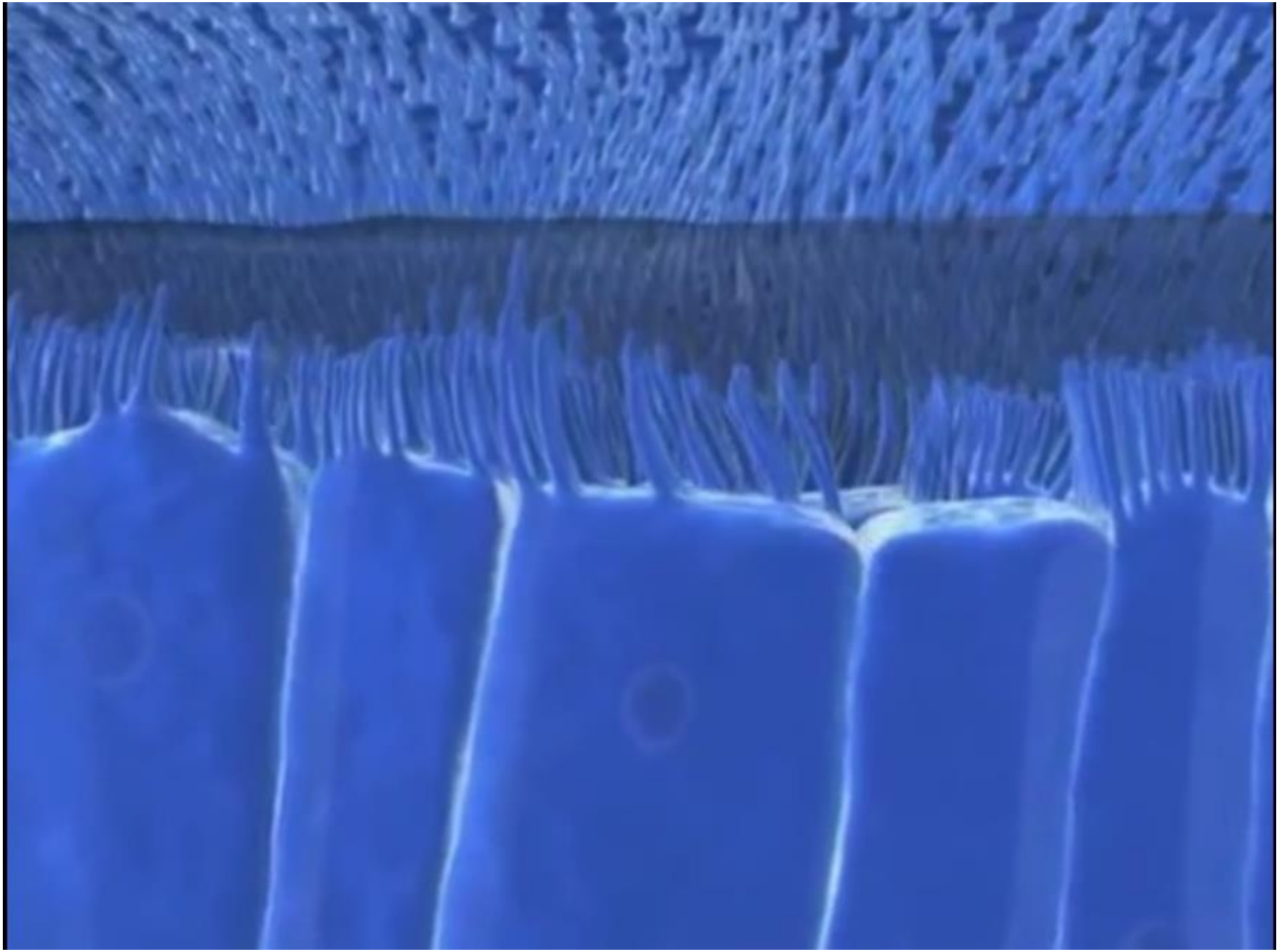
- The flow of ions from the cell and into this layer is determined by ion channels such as CFTR.
- CFTR not only allows chloride ions to be drawn from the cell and into the ASL, but it also regulates another channel called **ENaC** (**Epithelial Sodium Channel)**, which allows sodium ions to leave the ASL and enter the respiratory epithelium.
- *Epithelial sodium channels facilitate Na^+ reabsorption across the apical membranes of epithelia in the respiratory and reproductive tracts and exocrine glands.*
- CFTR normally inhibits this channel, but if the CFTR is defective, then sodium flows freely from the ASL and into the cell.

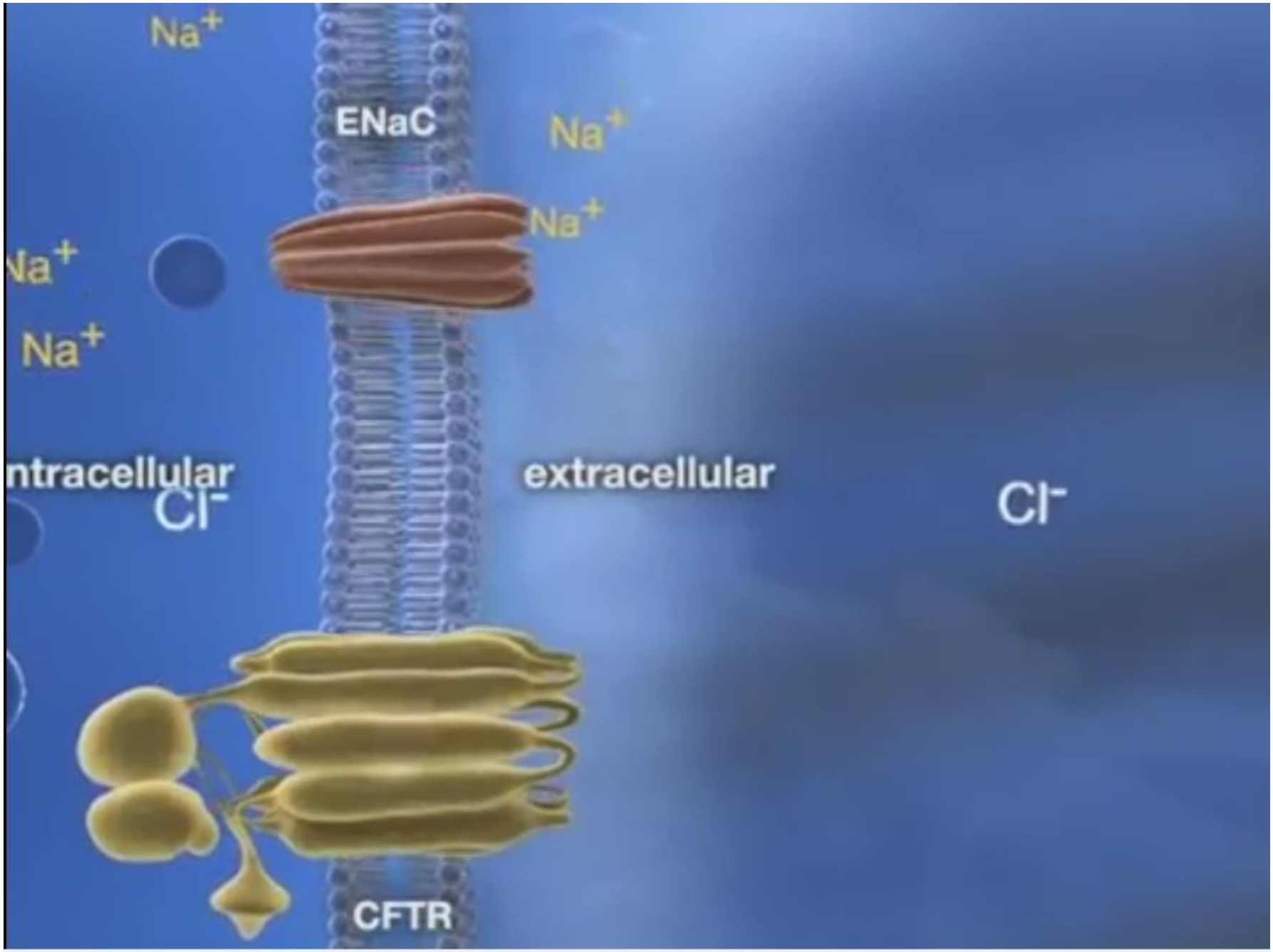
- As water follows sodium, the depth of ASL will be depleted and the cilia will be left in the mucous layer. As cilia cannot effectively move in a thick, viscous environment, mucociliary clearance is deficient and a buildup of mucus occurs, clogging small airways.

- The accumulation of more viscous, nutrient-rich mucus in the lungs allows bacteria to hide from the body's immune system, causing repeated respiratory infections.

- The presence of the same CFTR proteins in pancreatic duct and skin cells also cause symptoms in these systems.

- Defective CFTR results in decreased secretion of chloride and increased reabsorption of sodium and water across epithelial cells. The resultant reduced height of epithelial lining fluid and decreased hydration of mucus results in mucus that is stickier to bacteria, which promotes infection and inflammation.




Na+
ENaC
Na+
Na+
Na+
Na+
ntracellular
Cl-
extracellular
Cl-
CFTR