وَقُل رَّبِّ زِدْنِي عِلْمًا

النادي الطبي

RESPIRATORY SYSTEM

HAYAT BATCH

SUBJECT : Rs - Biochemistry

LEC NO. : 1

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Respiratory distress syndrome (RDS)

α1-Antitrypsin (α1- antiproteinase) deficiency

Cystic fibrosis

By

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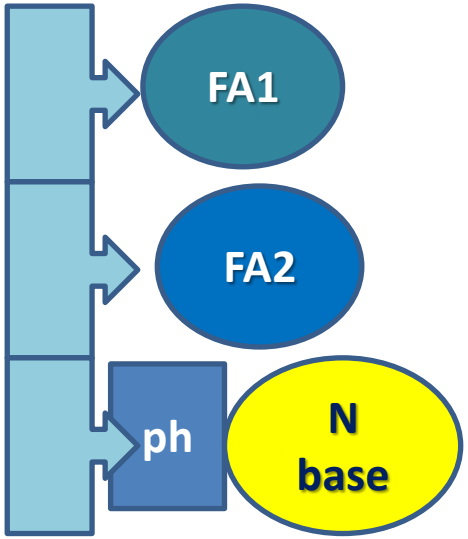
هي دي تدخل بتركيب مركب مهم أوي اللي هو (Lung surfactant)

لو نقص عند المريض بدخله في (RDS)

Phospholipids



Alcohol + FA (s) + phosphate + base

If the alcohol is glycerol ⟶ Glycerophospholipids = phosphoglycerides

If the alcohol is sphingosine ⟶ Sphingomylines

- Phospholipids are major components of the surfactant which if decreased, will lead to respiratory distress syndrome.
- Structure of phospholipids:

the backbone: alcohol (CH_2OH)

Position (1,2)

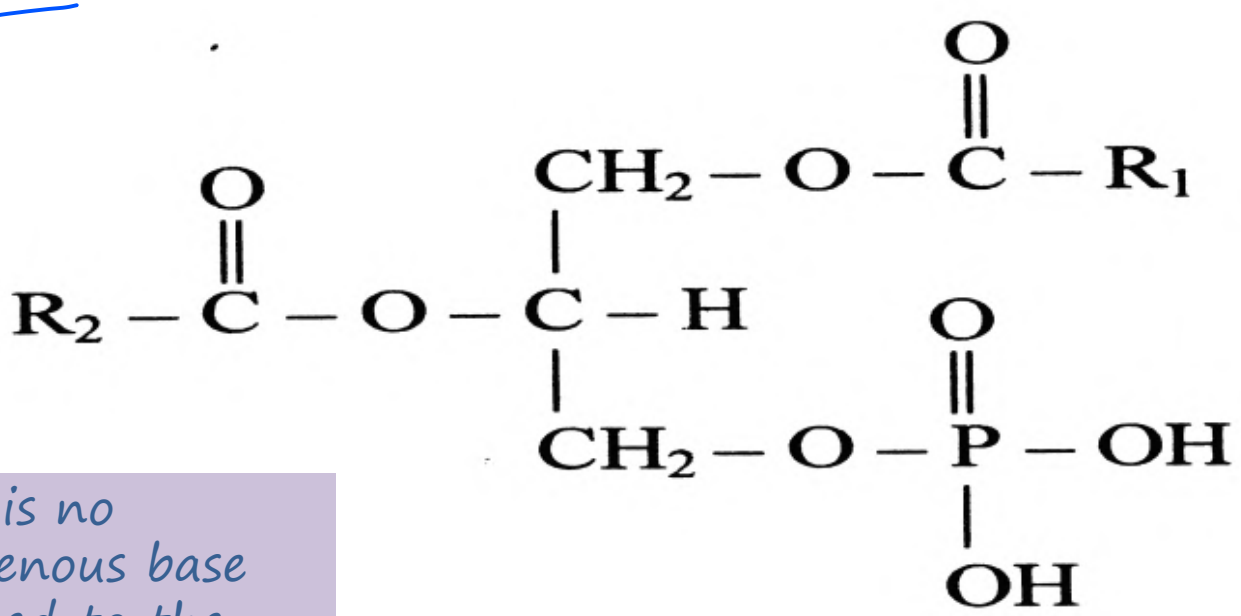
Two fatty acids and one phosphate group are bound to alcohol backbone.

Position (3)

a nitrogenous base attached to the phosphate group.

Phosphatidic acid:

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



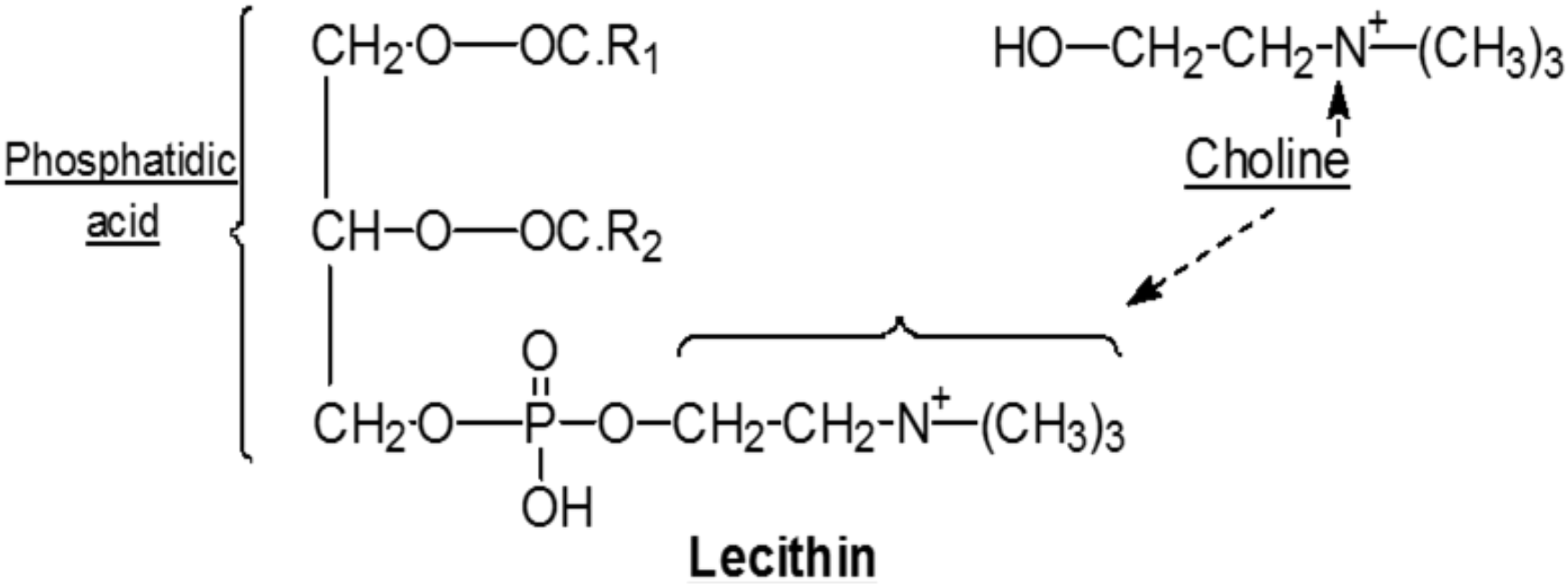
❖ There is no nitrogenous base attached to the phosphate group

- the linkage is Ester linkage

$R_{1,2}$: phosphate group

Phosphatidylcholine (lecithin): *the most important*

- The phosphate group of phosphatidic acid was esterified with choline



Lecithin

بتكوّنه الـ (Lung surfactant) ← طبقة المادة بتبطنه بتعمل (lining of alveoli) من غيرها بصير (collapse) يعني بتكسر

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 fluid 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.

- Palmitate = palmitic acid which is a fatty acid
- If palmitate is the fatty acid that is linked to glycerol → the phosphatidylcholine is called dipalmitoylphosphatidylcholine.
- Granular pneumocytes = type 2 pneumocytes
- The activity of lung surfactant is mainly dependent on DPPC.
- What is the meaning of (surfactant)??

surfactant means anti surface tension. So, it decreases the tension on the alveolar surface to prevent collapse.

- Full-term infant: الطفل الذي يولد تقريبا في الموعد المناسب
- The lung surfactant is completely formed in full-term infants.

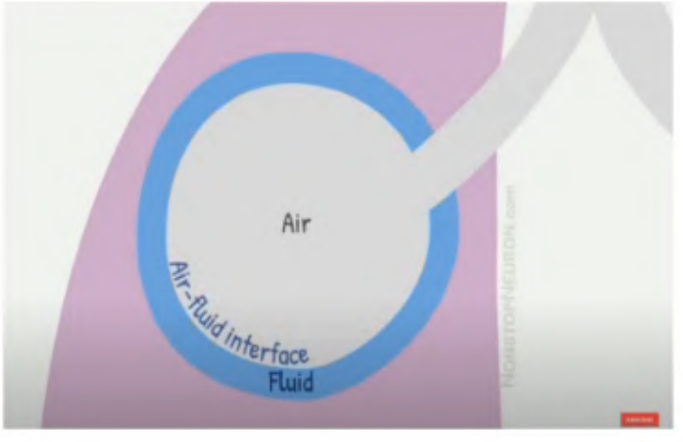
anti-surface tension

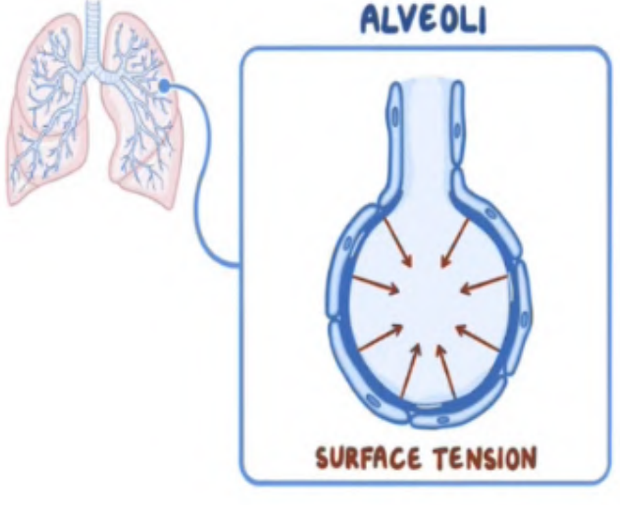
- Surfactant serves to decrease the surface tension of this fluid layer, reducing the pressure needed to reinflate alveoli, thereby preventing alveolar collapse (atelectasis).

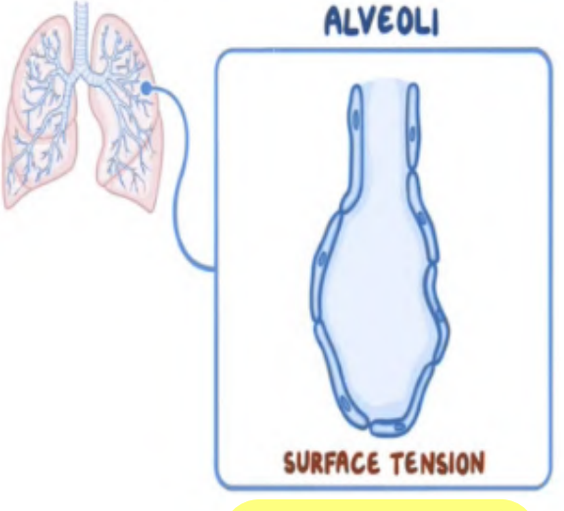
- **Respiratory distress syndrome (RDS)** in pre-term infants is associated with insufficient surfactant production, and is a significant cause of neonatal deaths in western countries.

(DPPC) بتكونله ما الحقت تصنع (Type II pneumocytes) الـ (بالرئة)

(surfactant) ما في :







(atelectasis)

- **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.

السائل اللي حوالين الجنين وهو اللي بنوخذ منه عينة للفحص

(L) is higher than (S)

- L/S ratio = lecithin / sphingomyline
- Before the 28th week of gestation, L/S = 1/1
- After 28 (or 32) weeks of gestation, L/S = 2/1
- If the ratio is above 2, this indicates a mature lung

- الأم الحامل اللي عندها (Diabetis / hyperglycemia) واللي عندها (uncontrol) ما توخذ انسولين بأثر على الـ (Lung surfactant) ليش؟ ببساطة لأنه الـ (glucose) يعوق الـ (placenta) على عكس الـ (insulin) اللي ما بقدر يخترقها فيصير عند الطفل فهو صوته رح يضطر يصير يصنع (insulin) بكميات كبيرة وهذا التصنيع بأثر على تصنيع الـ (Lung surfactant)

عكس الـ (insulin) عندنا هورمون (Glucocorticoids) اللي بعمل على زيادة وتسريع انتاج الـ (surfactant)

- 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.

- Immunosuppressive drugs are used in patients with autoimmune diseases or after transplantation surgeries.
- Chemotherapeutic drugs are used for cancer treatment.
- Chemotherapeutic and immunosuppressive drugs can damage pneumocytes that produce lung surfactant leading to respiratory distress syndrome which is called in this case (surfactant deficiency disorder).

α_1-Antitrypsin (α_1- antiproteinase)

- It is the chief **α_1 _ globulin.**
  - *Globulins: plasma proteins* (HLS) (أخذناه بالـ)
- **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.**

بكسر البروتينات بوجود هذا الإنزيم

ما بخليهم يكسروا البروتينات

- 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.** (لأنه فقدوا الـ (Elastesity) تاعته (الشهيق والزفير تاعه ضعيف جدا))
- Smoking inactivates α1- antiproteinase, which explains the occurance of emphysema in smokers.

- α_1Elastase enzyme is secreted by leukocytes to break down bacterial cell wall.
- Excess amounts of elastase destroys elastin in the lung tissue.
- Elastase amounts is controlled by alpha1-antitrypsin.
- Deficiency of alpha1-antitrypsin leads to damage of lung tissue → emphysema.

- Emphysema is **a lung condition that causes shortness of breath**

بأثر على (organs) كثير منهم خمنتهم وأعمارهم الـ (Lung) بسبب مشكلة بالـ (Air-way)

Cystic fibrosis

↳ Multy organ disscase

- It is an inherited autosomal recessive disorder
  - ❖ Autosomal recessive disorder: both copies of the gene must be defected to appear.
- Characterized by:
- Chronic bacterial infections of the airways and sinuses,
- Fat maldigestion due to pancreatic exocrine insufficiency,
  - ❖ Body secretions in cystic fibrosis patients are high in viscosity.
  - ❖ These secretions obstruct the pancreatic duct → 1) damage the pancreatic tissue 2) secretions cannot pass
- Infertility in males due to abnormal development of the vas deferens, *infertile not sterile (they have sperms)
- Elevated levels of chloride in sweat (>60mmol /L).
  - ❖ One of the tests for diagnosis of cystic fibrosis is the percentage of chloride in the sweat (diagnosis test)

بنظم دخول وخروج الـ (chloride)

- 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.

❖ Mutated CFTR lacks three bases encoded to phenylalanine.

❖ The resulting protein lacks the amino acid phenylalanine.

❖ لما نعمل ال (PCR) فال (size) تبع ال (جين) رح يكونه حجمه صغير لما يكونه (Mutated) لأنه إحنا حذفنا برتين

- *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.
  - *Cilia of epithelia cannot move due to dehydration and viscosity.*
- 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).

عشان زيادة اللزوجة فال(cillia) مارح تشتغل،مارح تعرف تتحرك وتطرد المواد الغريبة ومنضهي المواد

يوجد مضغات (البكتيريا رح تستغل الفرصة وتتغذى غاي وتسبب أمراضه

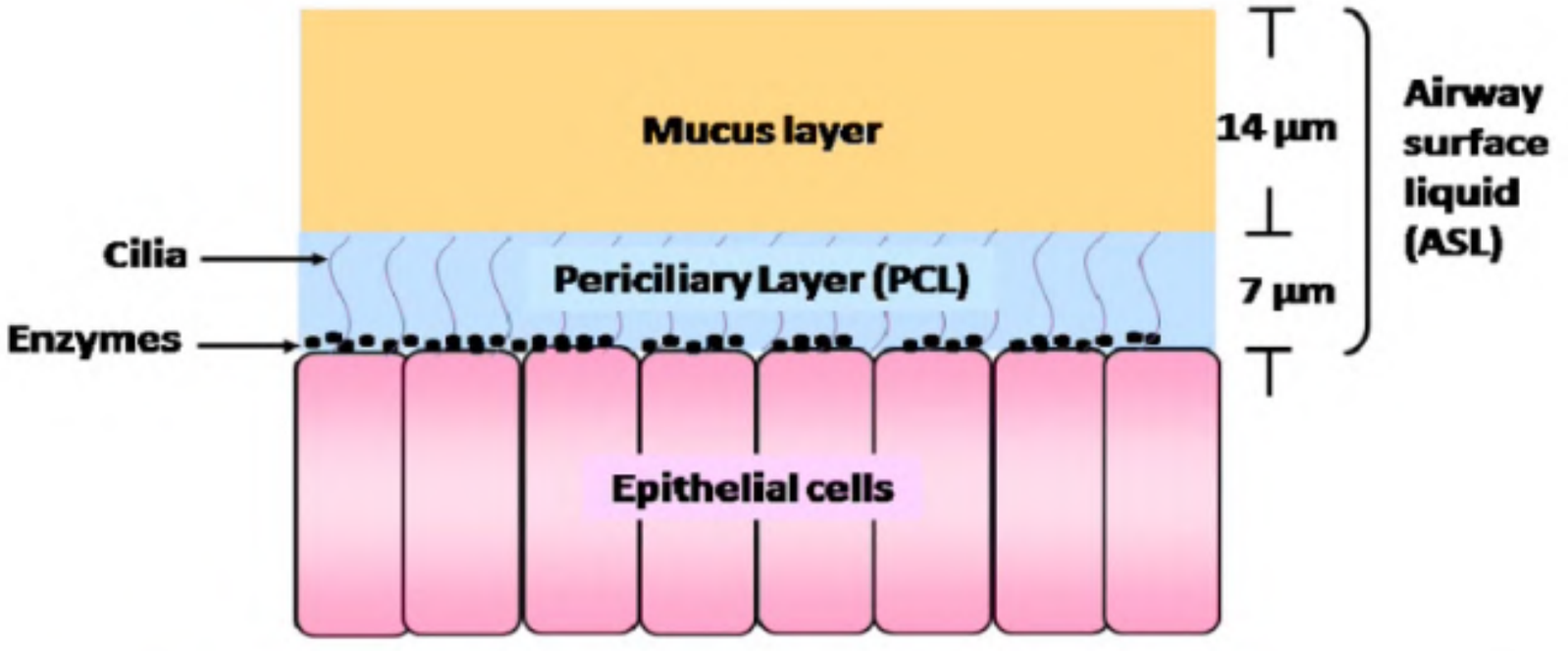


Figure 11: Layer structure of airway surface fluid (ASL) in human lungs. ASL is composed of two major layers: the mucus layer and the periciliary layer (PCL). PCL has similar thickness as cilia, which is about 7 micron. Mucus layer is approximately twice as thick as PCL.

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.

❖ *ASL: Airway surface liquid*

❖ *CFTR inhibits ENaC preventing the passage of d=sodium ions from ASL to the respiratory epithelium.*

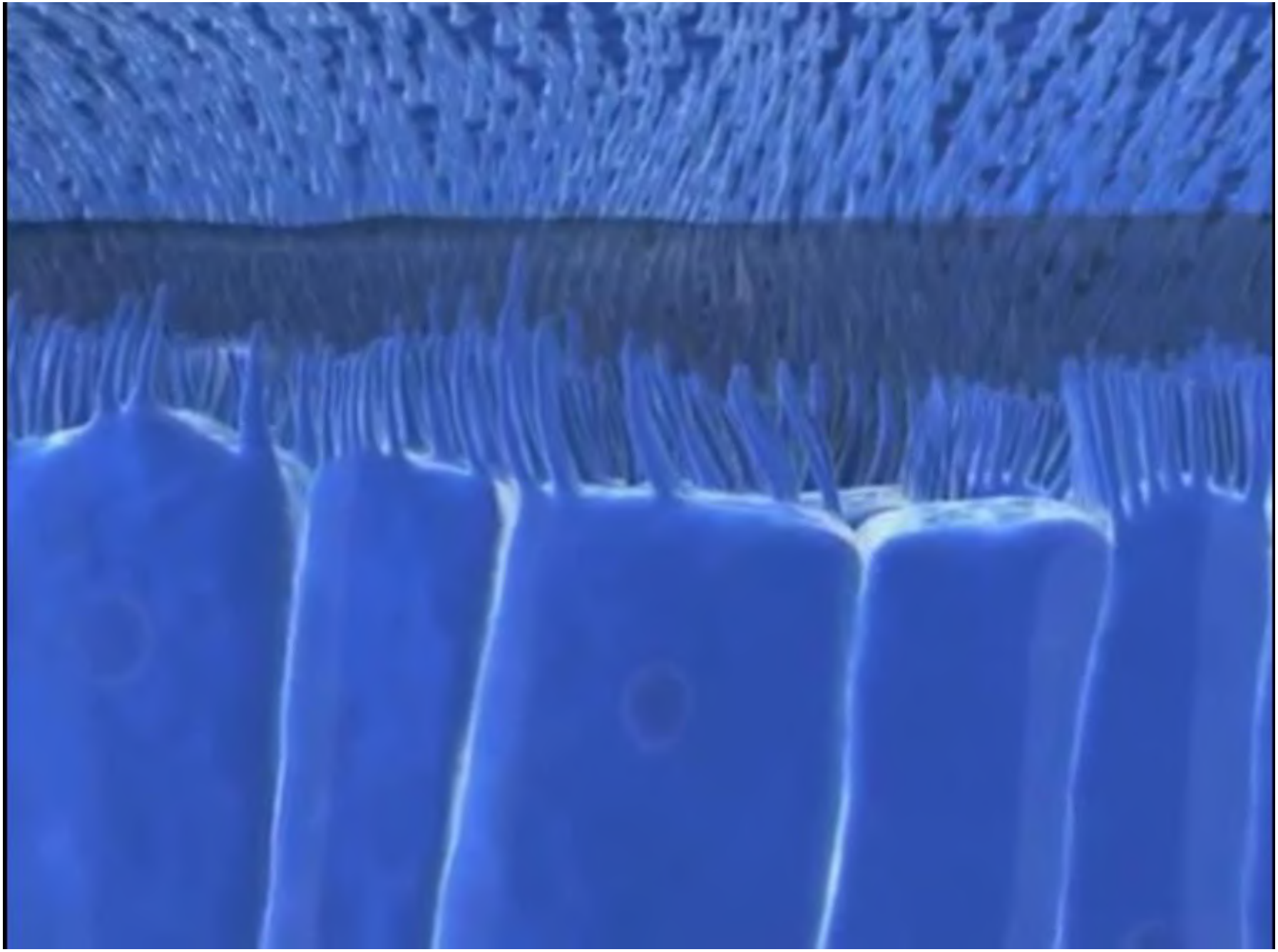
- *Epithelial sodium channels facilitate Na^+ reabsorption across the apical membranes of epithelia in the respiratory and reproductive tracts and exocrine glands.*
- CFTR normally inhibits this channel, but if the CFTR is defective, then sodium flows freely from the ASL and into the cell.

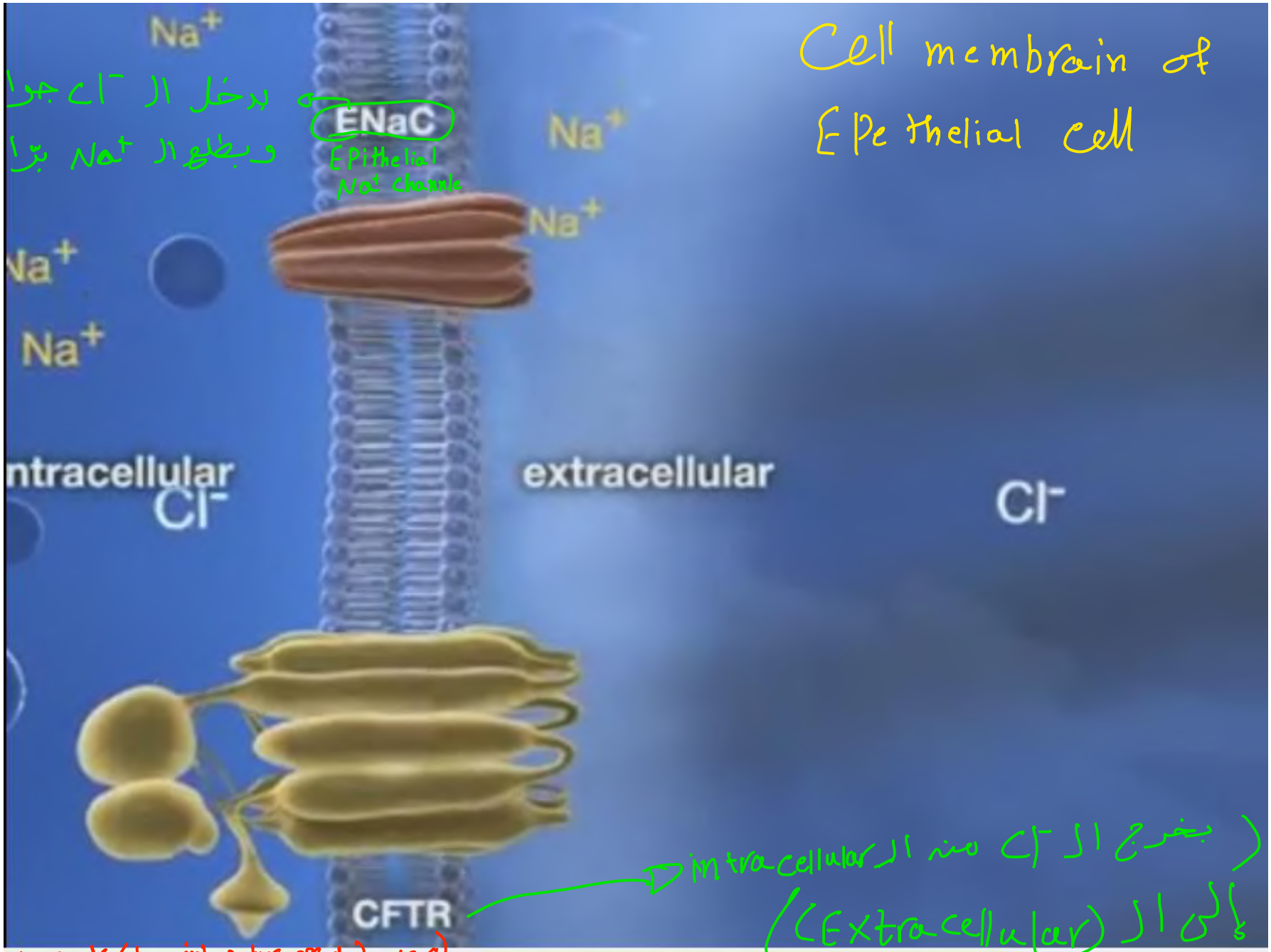
- As water follows sodium, the depth of ASL will be depleted and the cilia will be left in the mucous layer. As cilia cannot effectively move in a thick, viscous environment, mucociliary clearance is deficient and a buildup of mucus occurs, clogging small airways.

- 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.




Cell membrain of Epethelial cell
Na+
ENaC
Epithelial Na+ channle
Na+
Na+
Na+
Na+
ntracellular
Cl-
extracellular
Cl-
CFTR
intracellular
extracellular

- لو ال (CFTR) خربانة هل رح يعرف يطلّع ال Cl^- إلى ال (ECF)؟ لا طبعاً رح يكونه (low inhepatory effect) على ال (ENaC)؟ برضه لا. حيب شو نتيجة هاي المشكلة؟ رح يتراكم ال Cl^- جوا الخلية وال (Na^+) جوّا الخلية برضه لأنه مافي اشي يطلعه مما يؤدي إلى سحب ال (water) إلى داخل الخلية بفعل ال (Na^+) و ال (Cl^-) فيؤدي إلى (Dehydration for fluid lins of Ear way) يعني زودنا ال (Viscosity) ال (ECF).

بترا الخلية

اللهم صلِّ وسلم وبارك على محمد وعلى آله وأصحابه أجمعين