

Cystic Fibrosis Gene: Normal Structure and Function

CFTR domains · regulated gating · tissue-specific epithelial transport

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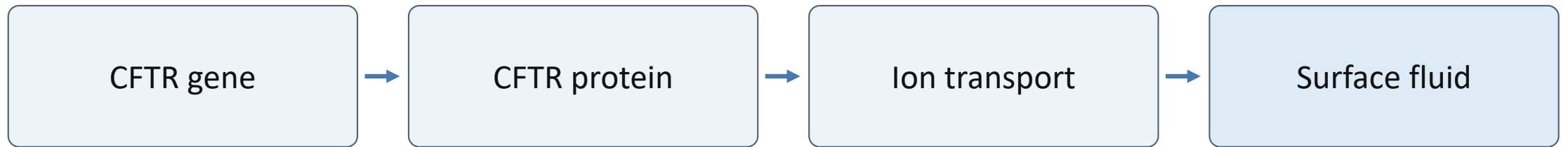
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Learning objectives

- Identify the CFTR gene locus and five major protein domains.
- Explain phosphorylation- and ATP-dependent CFTR gating.
- Compare CFTR roles in airway, intestine, and sweat duct.
- Relate bicarbonate transport to secretion and mucin behavior.

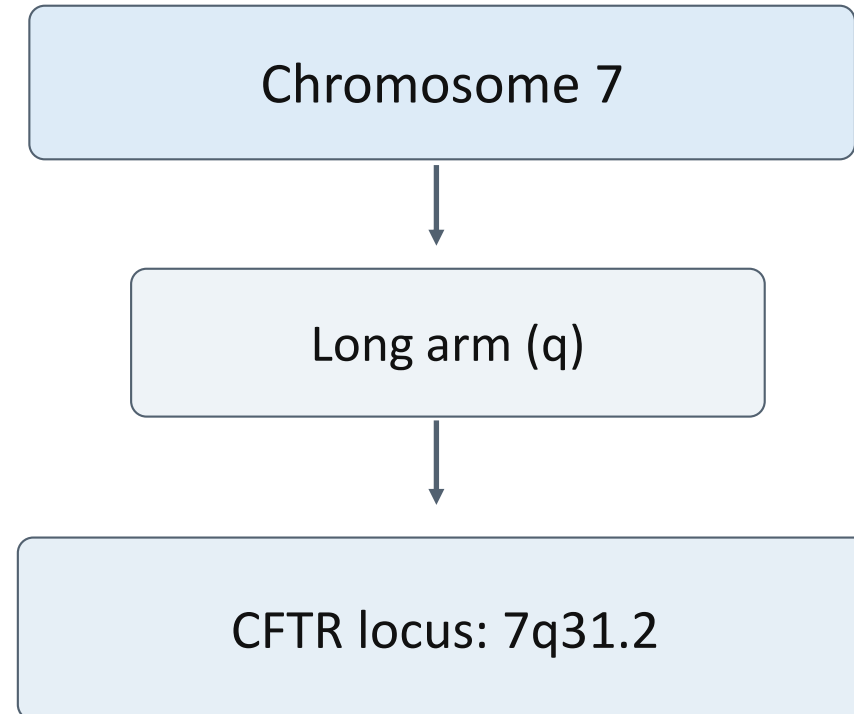
CFTR connects a gene to epithelial fluid physiology



- A single gene encodes an apical epithelial anion channel.
- Channel conductance and transport regulation determine surface-fluid conditions.
- The physiological effect depends on the epithelial tissue.

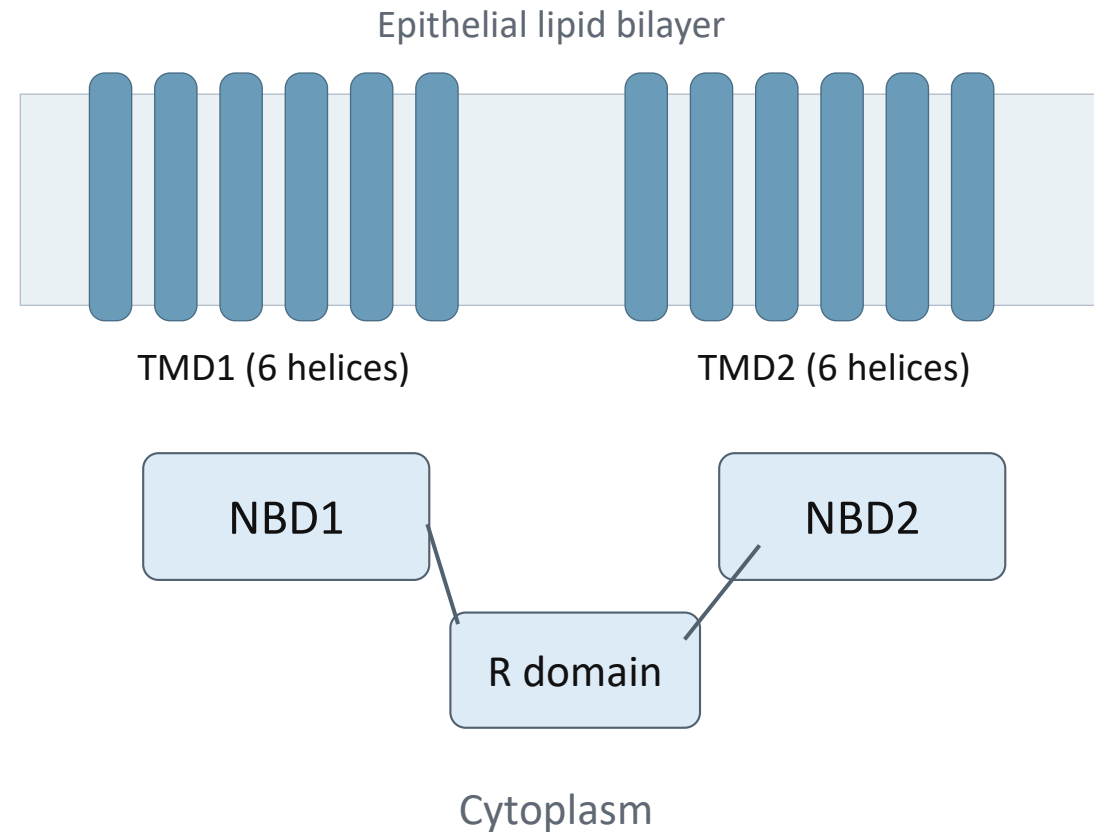
The CFTR locus is on chromosome 7

- The cystic fibrosis transmembrane conductance regulator gene is at 7q31.2.
- Its protein product regulates epithelial chloride and bicarbonate transport.
- Chromosomal location identifies the gene; It does not explain channel gating.



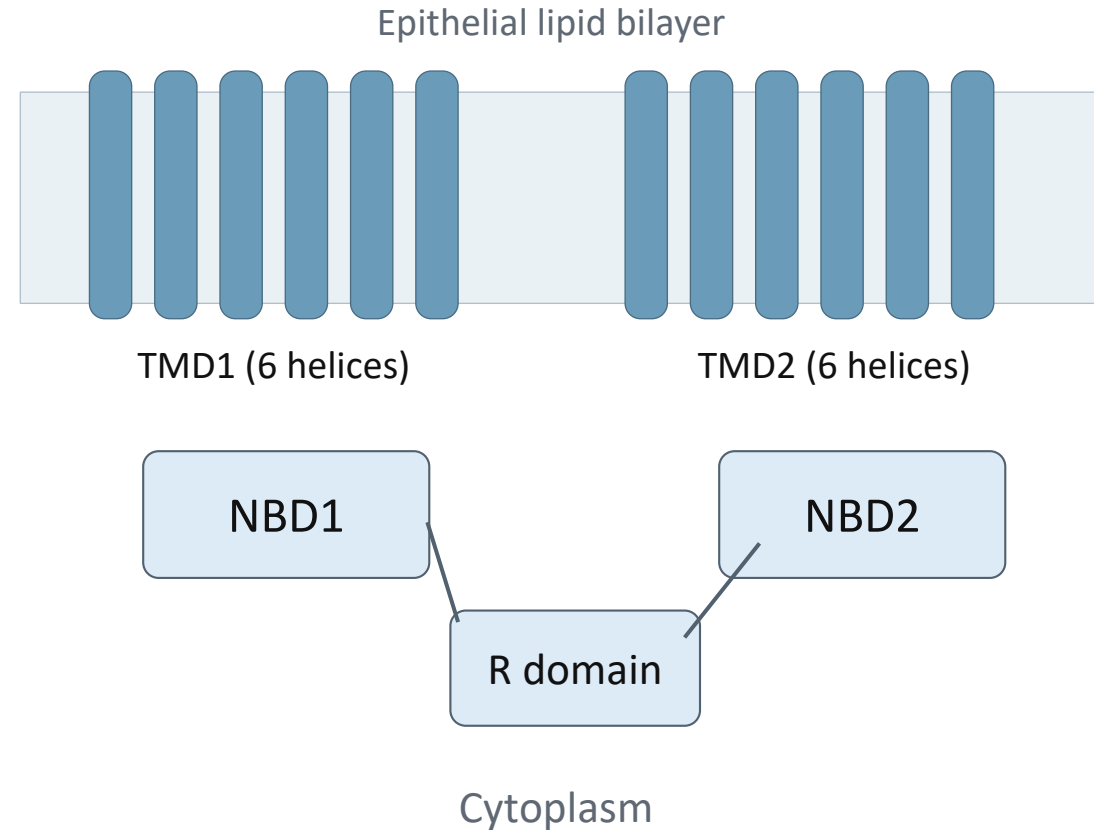
One CFTR gene produces a multidomain protein

- CFTR encodes a polypeptide containing 1480 amino acids.
- Distinct protein domains carry out pore formation and regulation.
- The major architecture can be grouped into five functional domains.



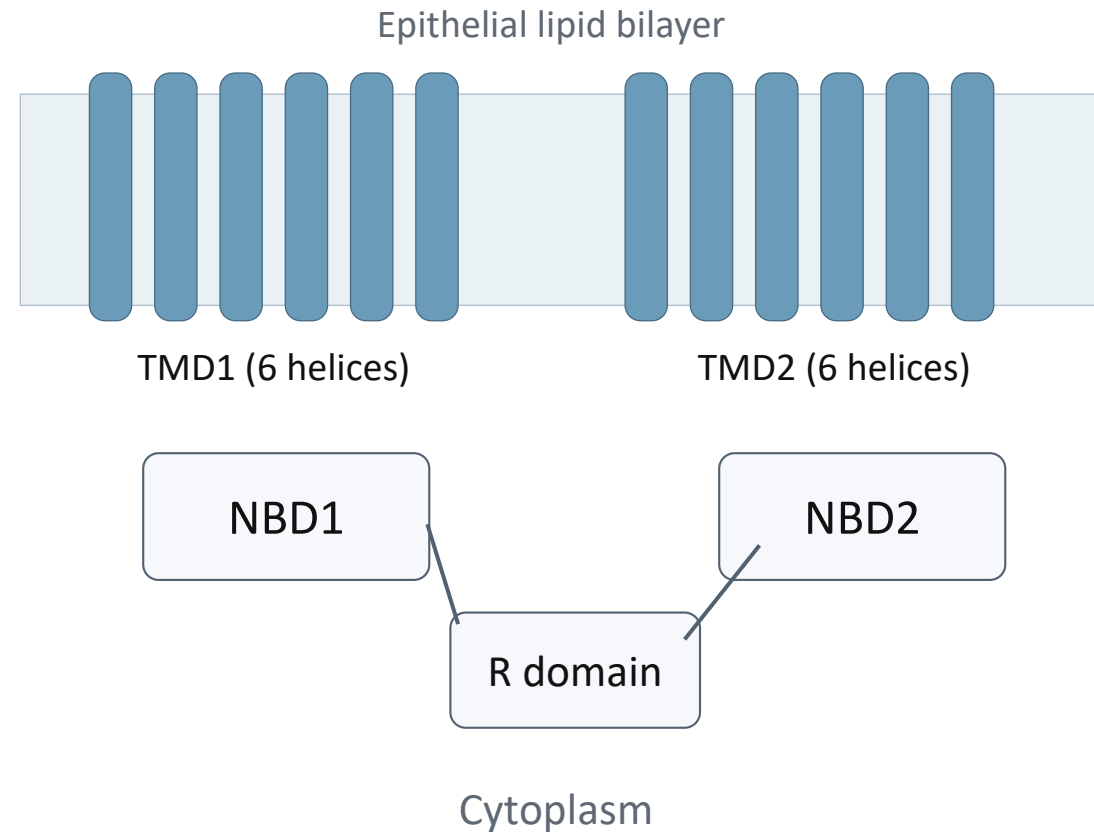
The five-domain CFTR architecture

- Two transmembrane domains form the channel-bearing portion.
- Two nucleotide-binding domains respond to ATP.
- One regulatory (R) domain contains kinase phosphorylation sites.



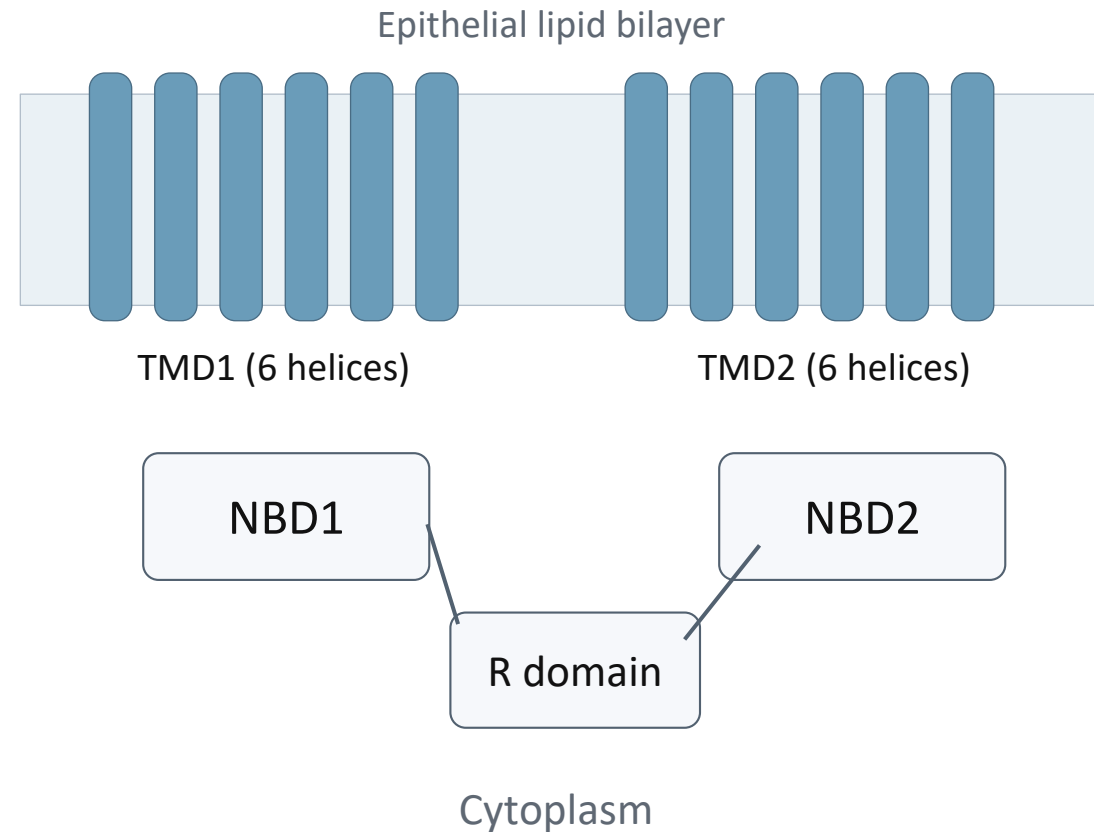
Transmembrane domains traverse the lipid bilayer

- CFTR has two transmembrane domains, TMD1 and TMD2.
- Each domain contains six α -helices.
- Together, these membrane-embedded structures help form the anion pore.



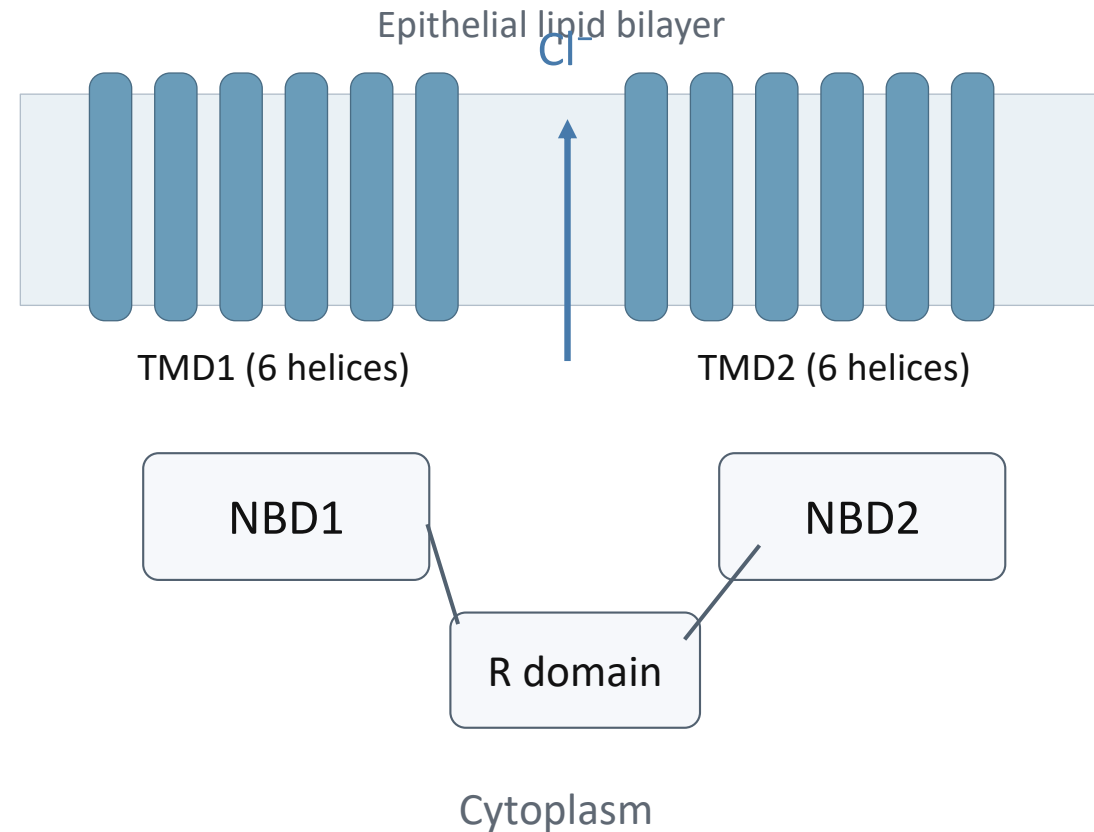
Twelve membrane-spanning helices organize the pore

- Six helices belong to the first transmembrane domain.
- Six helices belong to the second transmembrane domain.
- The paired domain architecture provides the pathway for chloride passage.



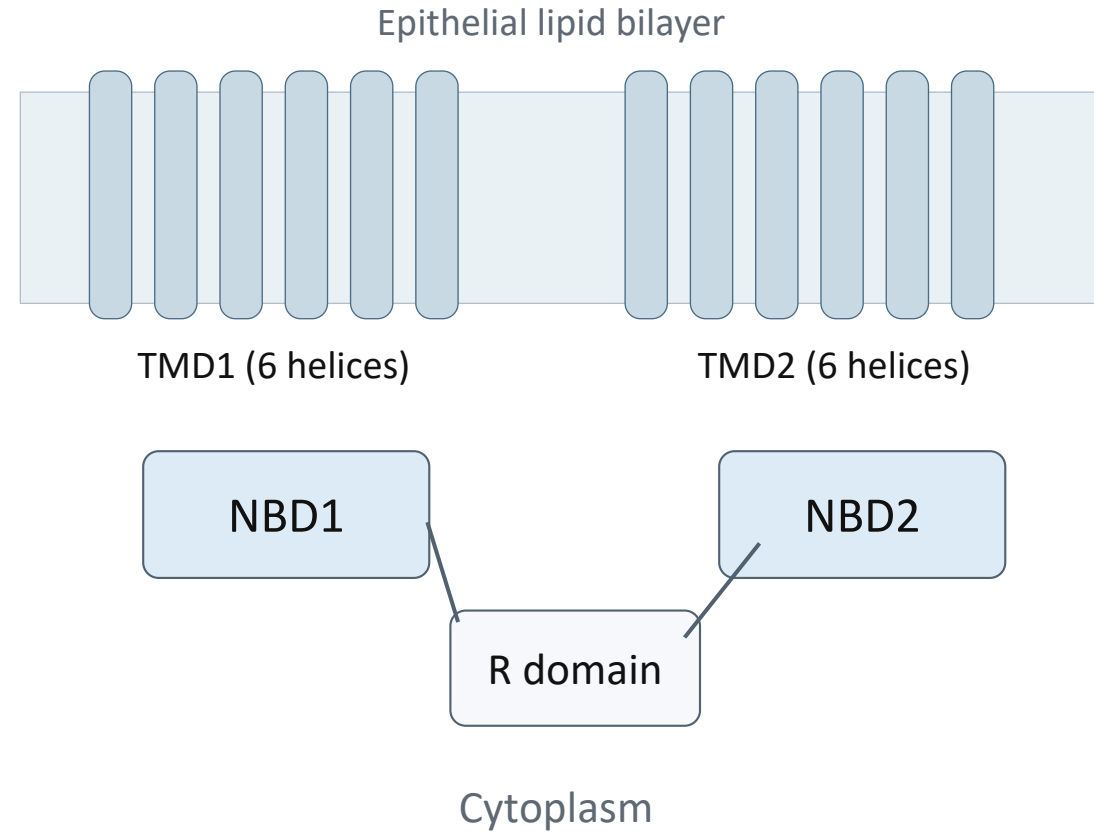
The pore provides an anion-conduction pathway

- The transmembrane domains form the channel through which chloride passes.
- A permeation pathway is distinct from the signals that govern pore opening.
- Transport requires a channel at the appropriate epithelial membrane.

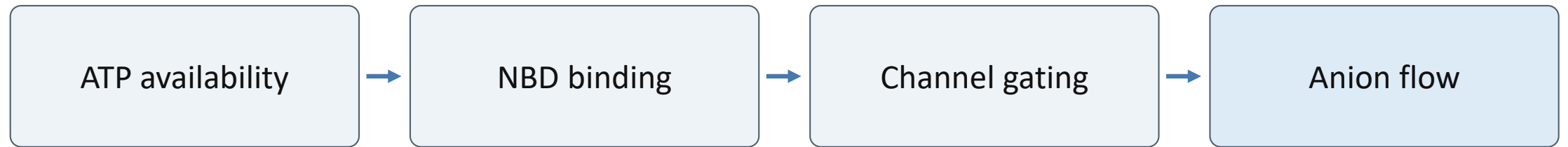


NBD1 and NBD2 are cytoplasmic domains

- CFTR contains two cytoplasmic nucleotide-binding domains.
- These domains interact with adenosine triphosphate (ATP).
- ATP-dependent domain activity contributes to opening and closing of the pore.



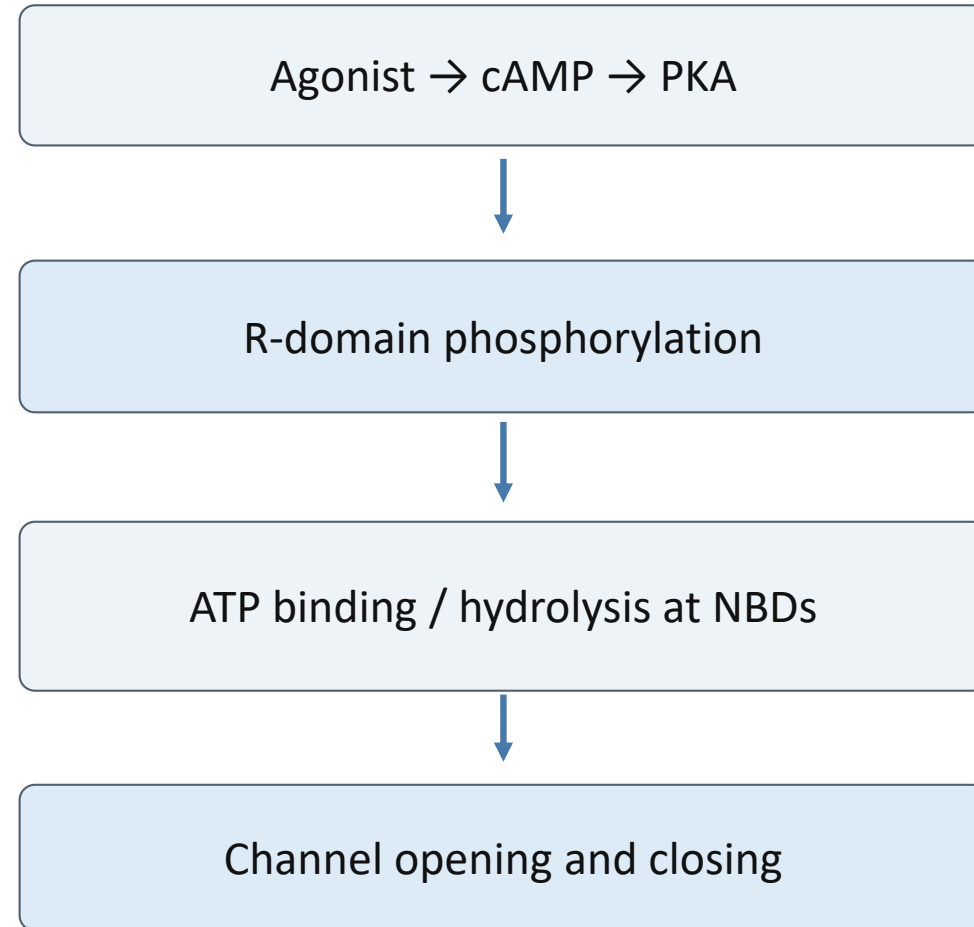
ATP binding is essential to CFTR gating



- ATP binding occurs at the nucleotide-binding domains.
- This activity is necessary for normal channel opening and closing.
- ATP is therefore a gating requirement, not merely a metabolic background factor.

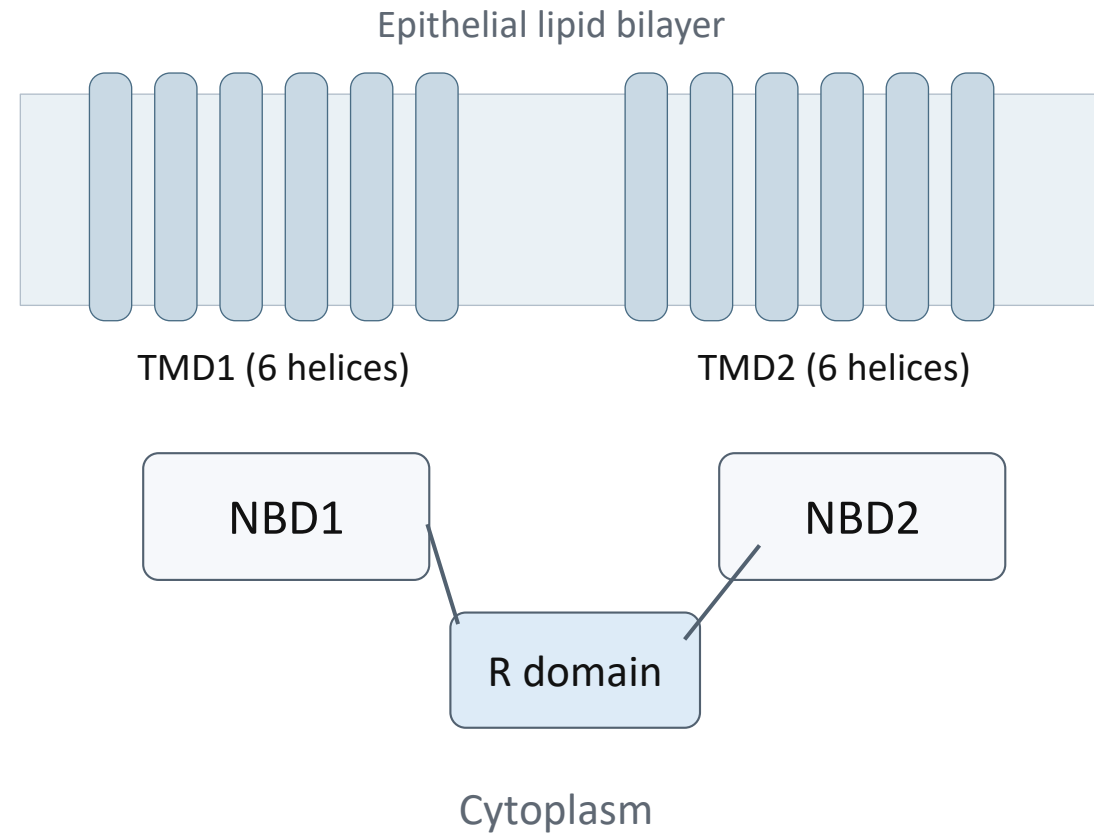
ATP hydrolysis participates in pore cycling

- ATP hydrolysis occurs at the NBDs.
- Binding and hydrolysis together support channel opening/closing.
- The kinetic cycle is regulated further by phosphorylation of the R domain.



The regulatory domain controls activation

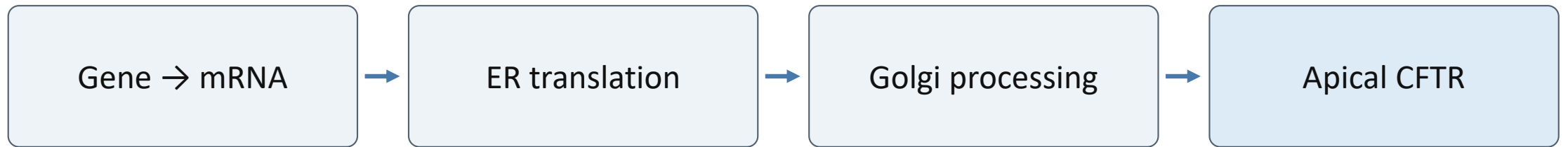
- The R domain is distinct from the TMDs and NBDs.
- It contains phosphorylation sites for protein kinase A (PKA).
- R-domain phosphorylation enhances ATP-dependent channel activity.



CFTR architecture separates three tasks

Domain	Structural identity	Main function
TMD1 + TMD2	Two × six α -helices	Anion pore
NBD1 + NBD2	Cytoplasmic domains	ATP-dependent gating
R domain	PKA sites	Regulatory phosphorylation

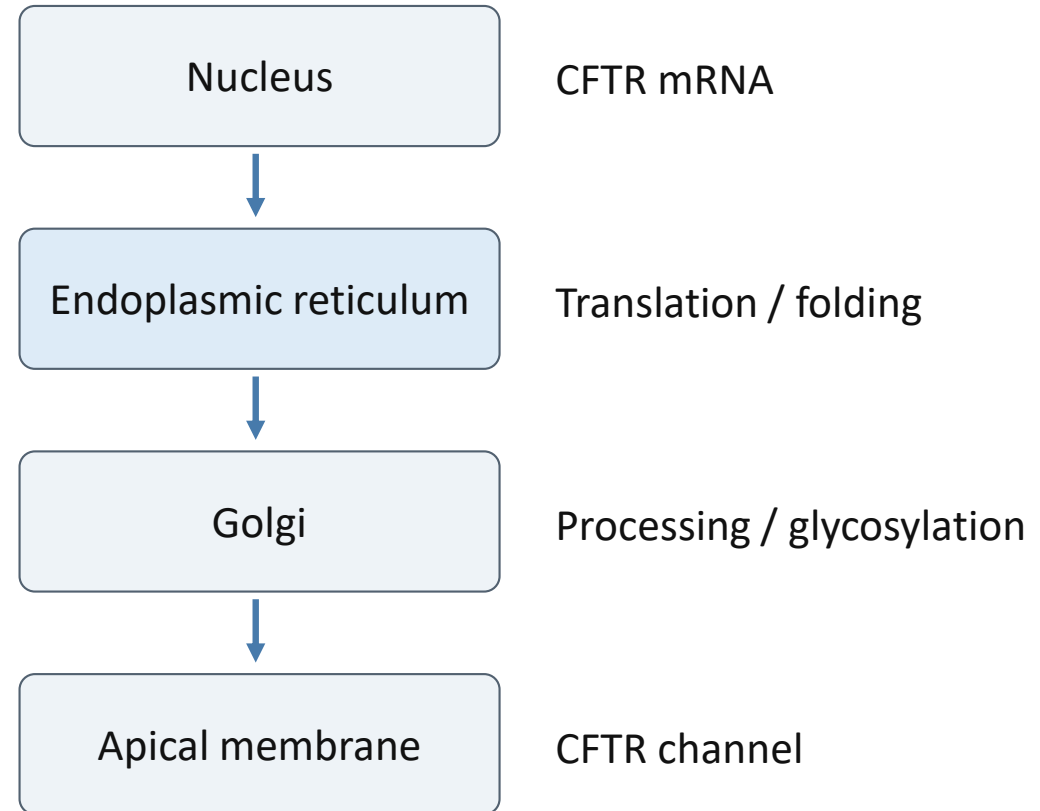
Biosynthesis begins before membrane transport



- The CFTR gene is transcribed into mRNA.
- Translation and folding occur in the endoplasmic reticulum.
- Processing and glycosylation precede delivery of mature CFTR to its membrane location.

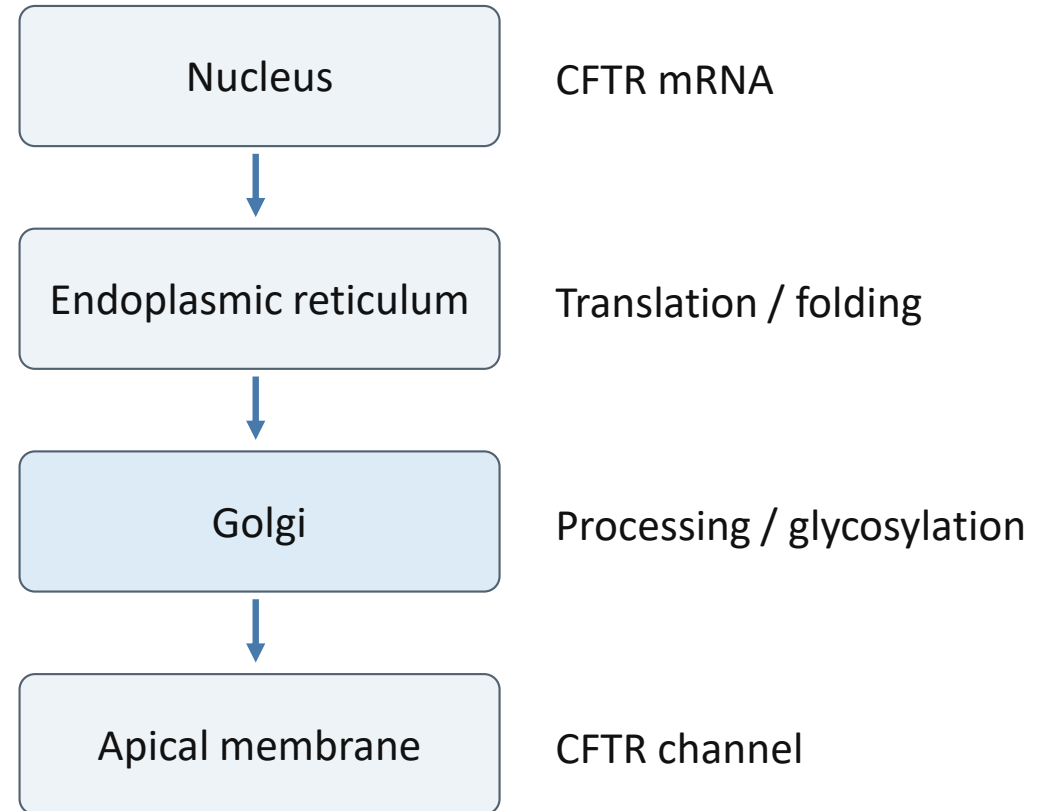
CFTR is synthesized and folded in the ER

- Translation converts CFTR mRNA into the polypeptide.
- Protein folding occurs in the endoplasmic reticulum.
- Proper biosynthetic processing is relevant to how the channel reaches the cell surface.



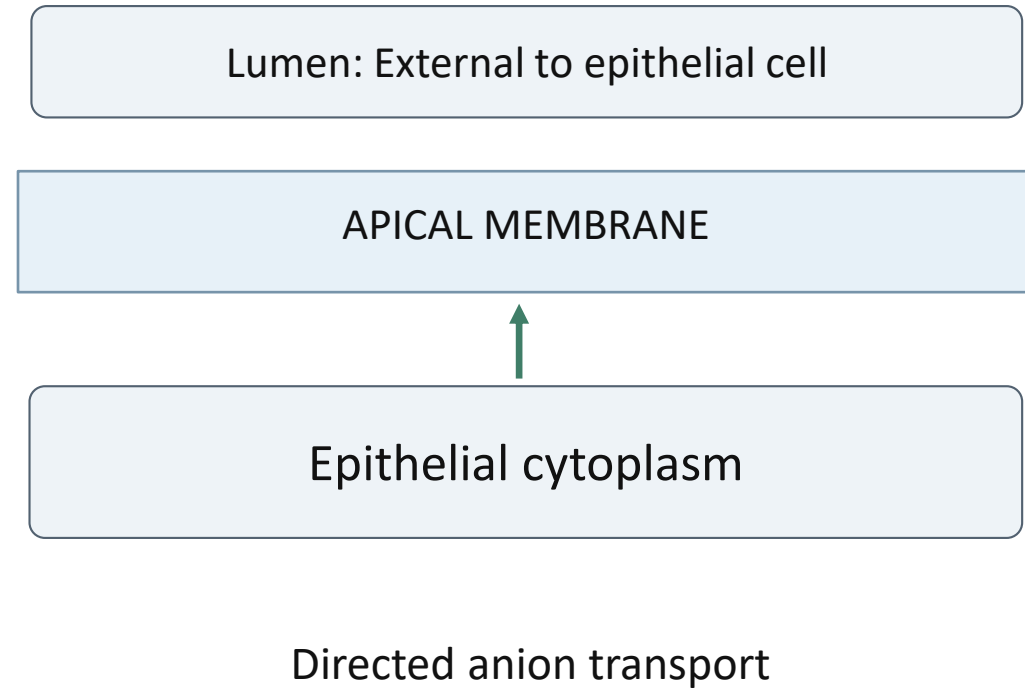
Golgi processing precedes mature surface CFTR

- The biosynthetic pathway includes Golgi processing.
- CFTR undergoes glycosylation along the maturation route.
- The final functional destination is the epithelial cell membrane.

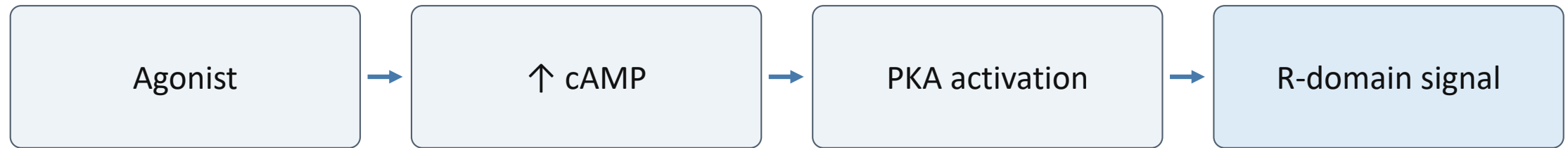


Apical localization enables directional transport

- CFTR operates at the luminal (apical) epithelial surface.
- The luminal compartment differs between an airway and a sweat duct.
- The same protein can consequently participate in secretion or reabsorption.



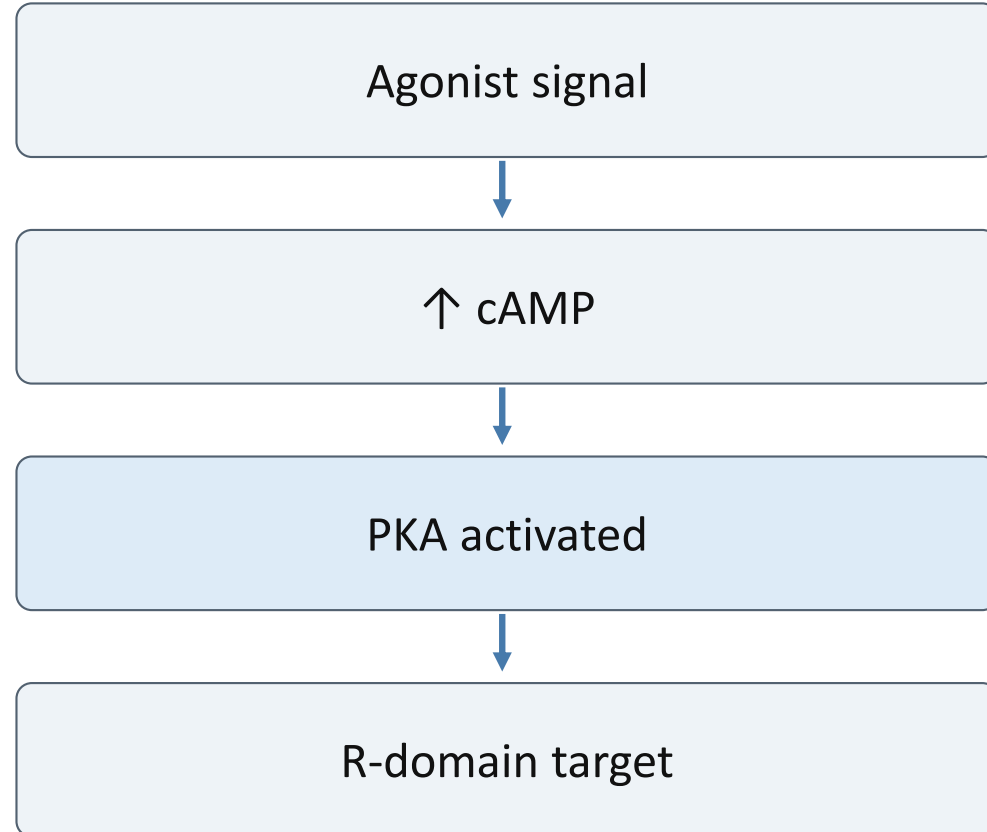
Channel activation begins with a signaling agonist



- An extracellular agonist initiates an epithelial signaling response.
- The response increases intracellular cyclic AMP (cAMP).
- This signaling step precedes activation of protein kinase A.

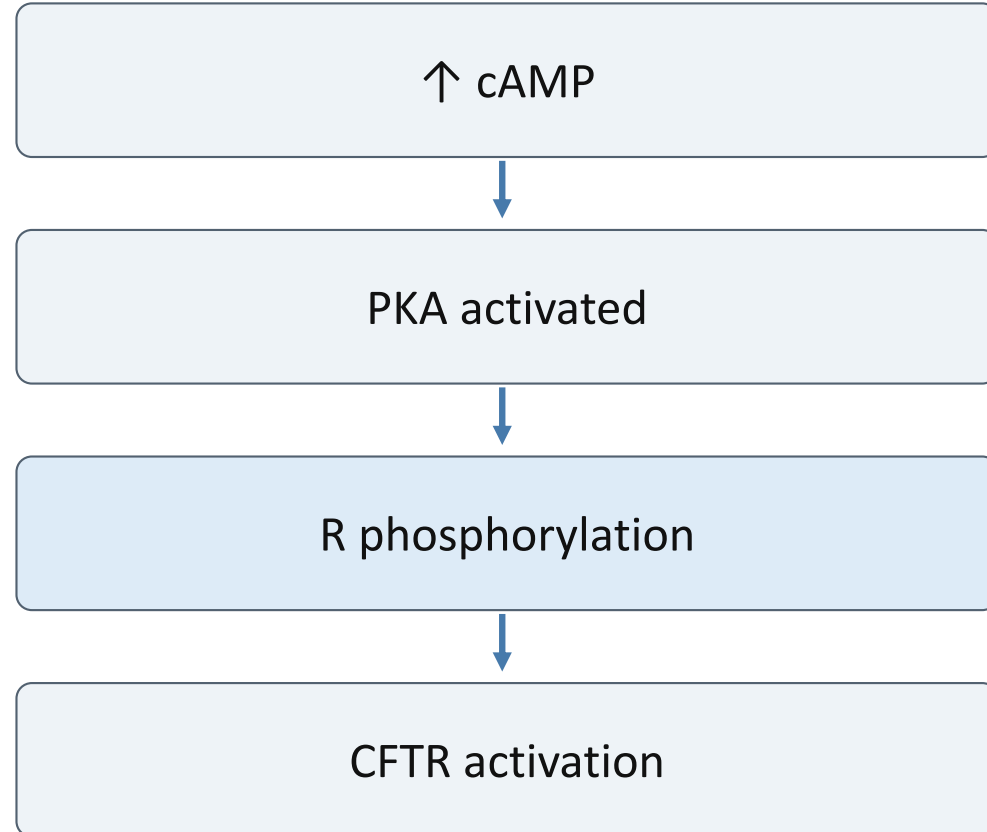
CAMP links a receptor signal to the channel

- Cyclic AMP is the intracellular signal described for CFTR activation.
- Increased cAMP activates protein kinase A.
- The cAMP step translates cellular stimulation into channel regulation.



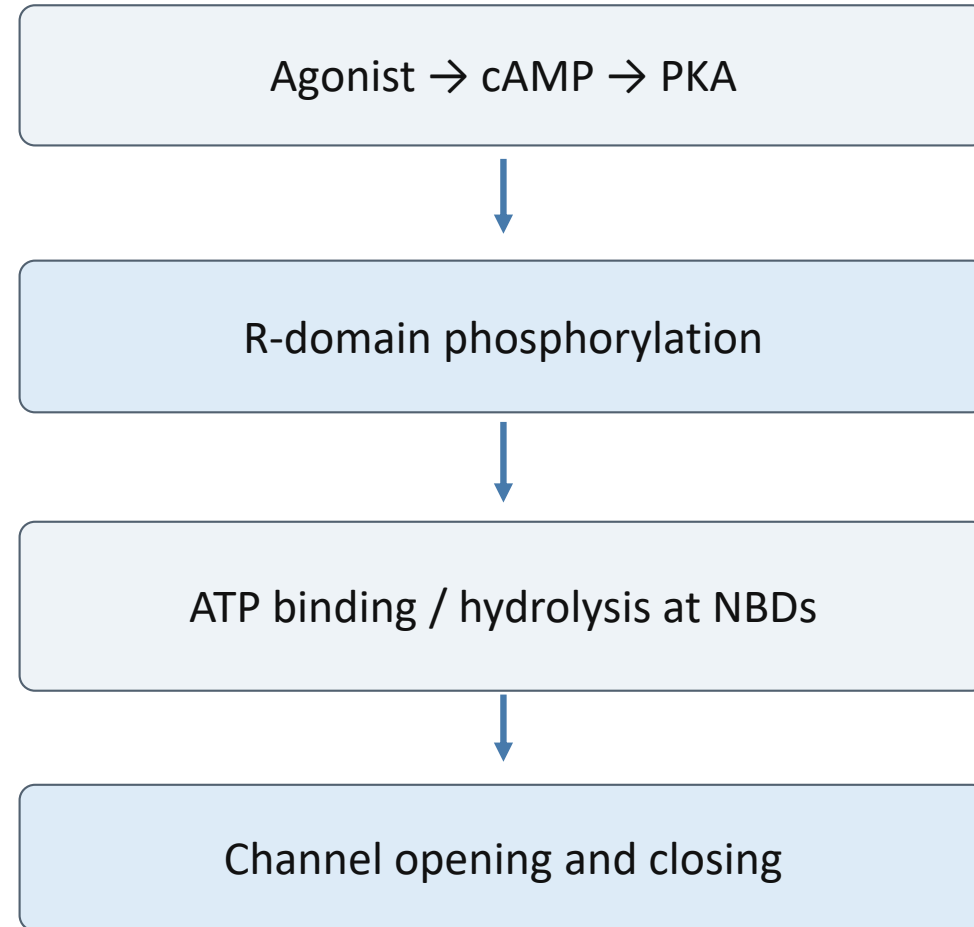
Protein kinase A targets the R domain

- Activated PKA phosphorylates R-domain sites.
- Phosphorylation enhances channel opening in the presence of ATP.
- Thus, a protein kinase links signaling to the pore.

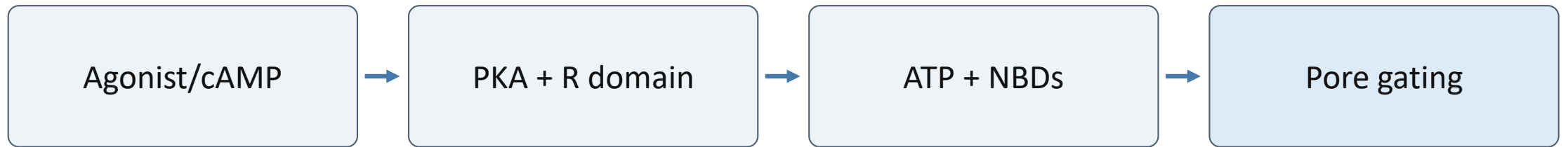


Phosphorylation and ATP regulate the same pore

- R-domain phosphorylation promotes channel activation.
- ATP binding/hydrolysis at NBDs supports the opening–closing cycle.
- Neither mechanism should be confused with the ion pathway in the TMDs.



The full gating sequence is a coupled process



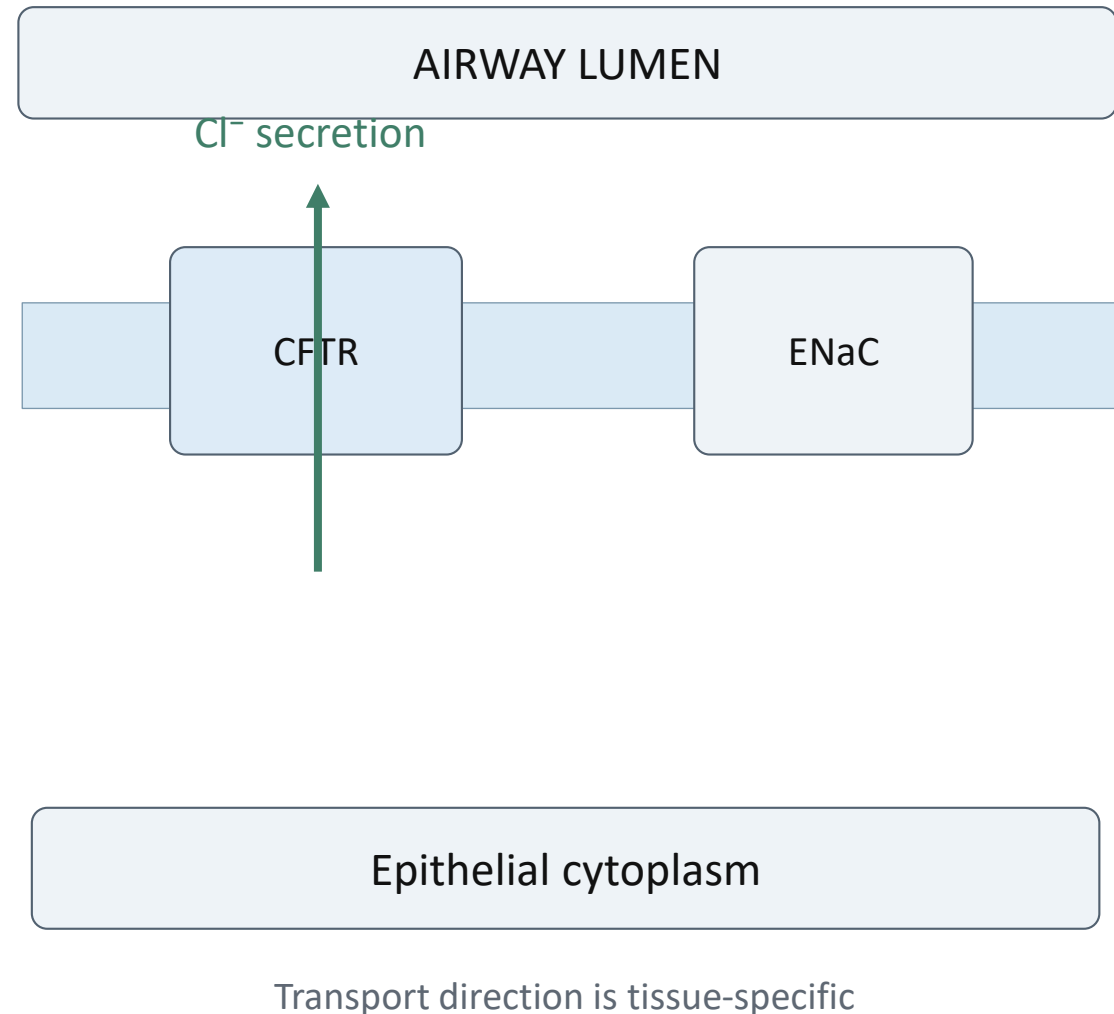
- Agonist → cAMP → PKA occurs upstream.
- PKA phosphorylates the regulatory domain.
- ATP-dependent NBD behavior then supports pore opening and closing.

Activation differs from permeation

Question	Gating	Permeation
What changes?	Open/closed state	Ion movement
Key domains	R domain + NBDs	TMD1 + TMD2
Main inputs	PKA phosphorylation, ATP	Electrochemical conditions

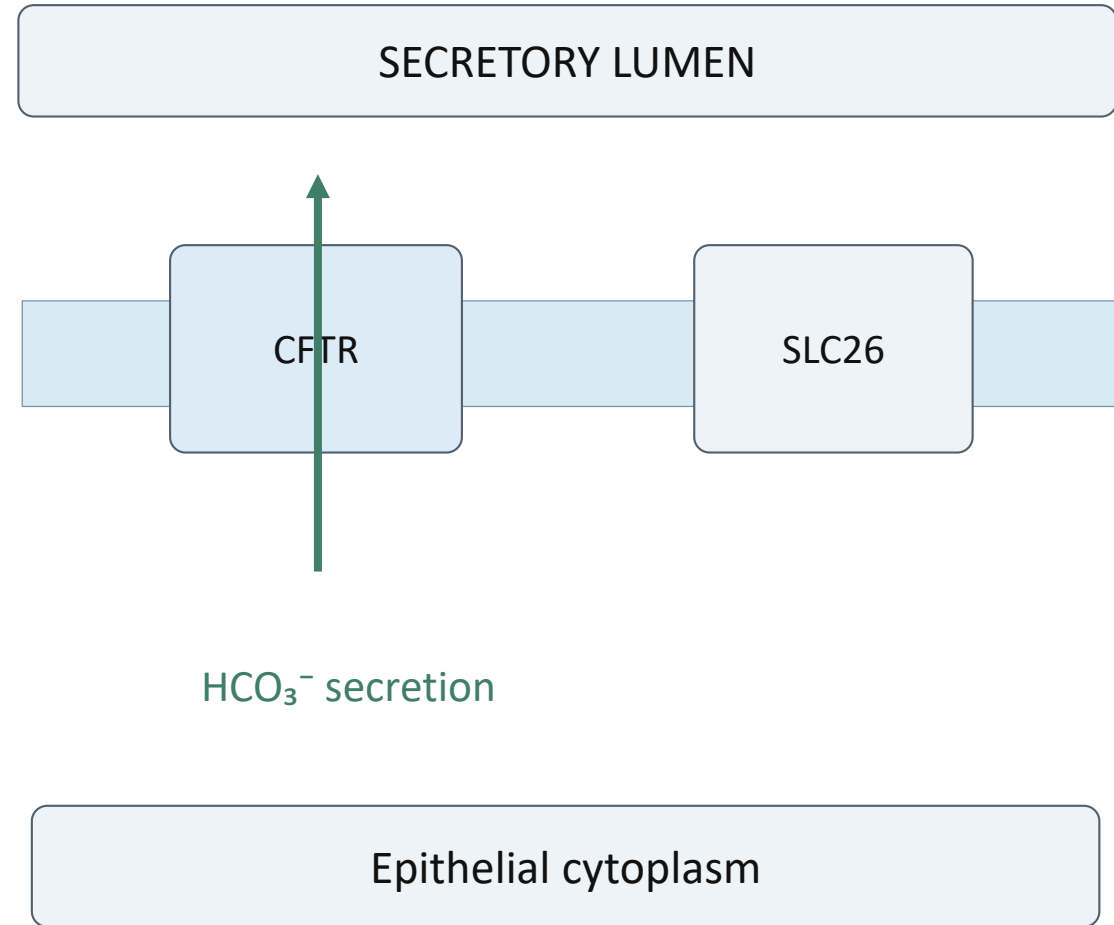
CFTR conducts chloride across the epithelium

- CFTR was initially characterized as a chloride-conductance channel.
- The direction of net transport is tissue-dependent.
- Chloride movement contributes to luminal electrolyte and water balance.



CFTR also transports bicarbonate

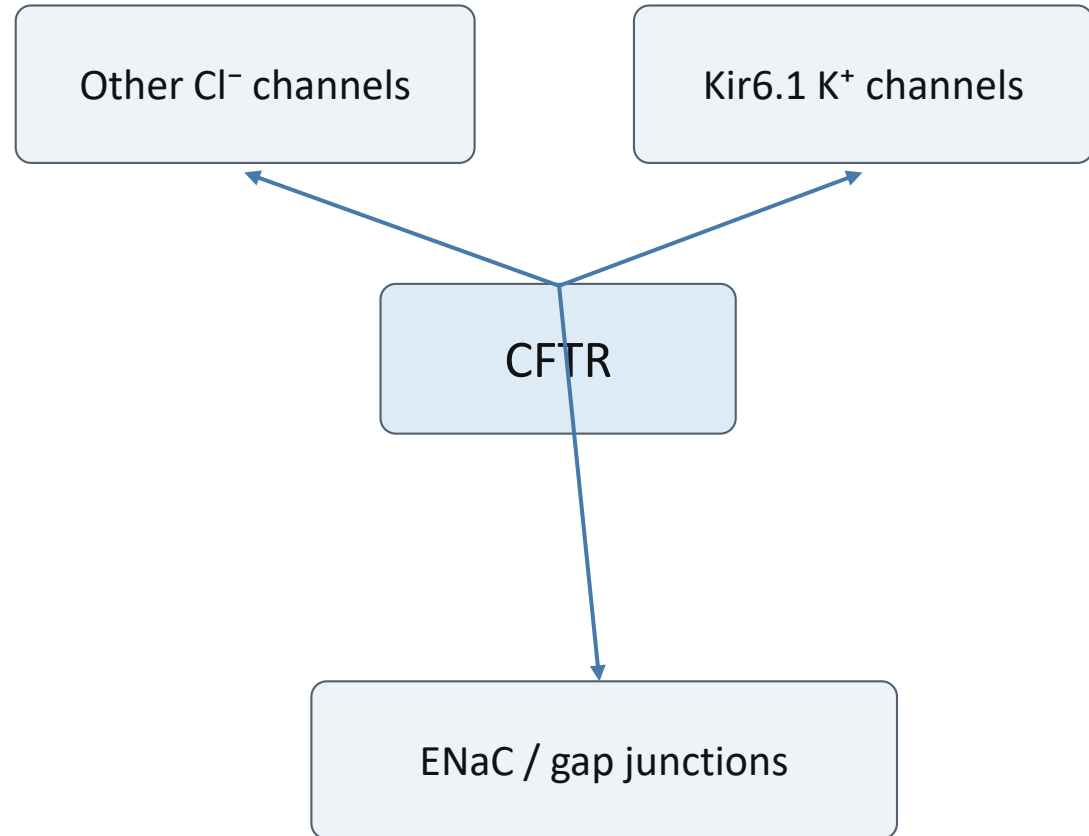
- The CFTR pore is not completely selective for chloride.
- Bicarbonate (HCO_3^-) can also pass through the channel.
- Bicarbonate transport changes the acid–base character of secretions.



Transport direction is tissue-specific

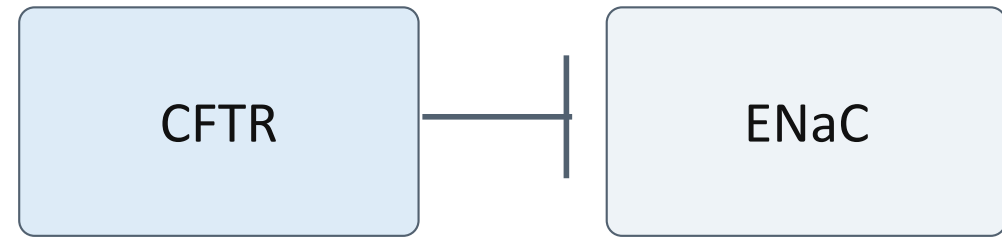
CFTR has functions beyond its own pore

- CFTR regulates other ion channels and cellular processes.
- Effects involving chloride, potassium, and gap-junction channels.
- Other regulated processes include ATP transport and mucus secretion.



The ENaC interaction is physiologically important

- ENaC is the epithelial sodium channel at the apical surface.
- It mediates uptake of sodium from luminal fluid.
- The relationship between CFTR and ENaC differs by tissue.



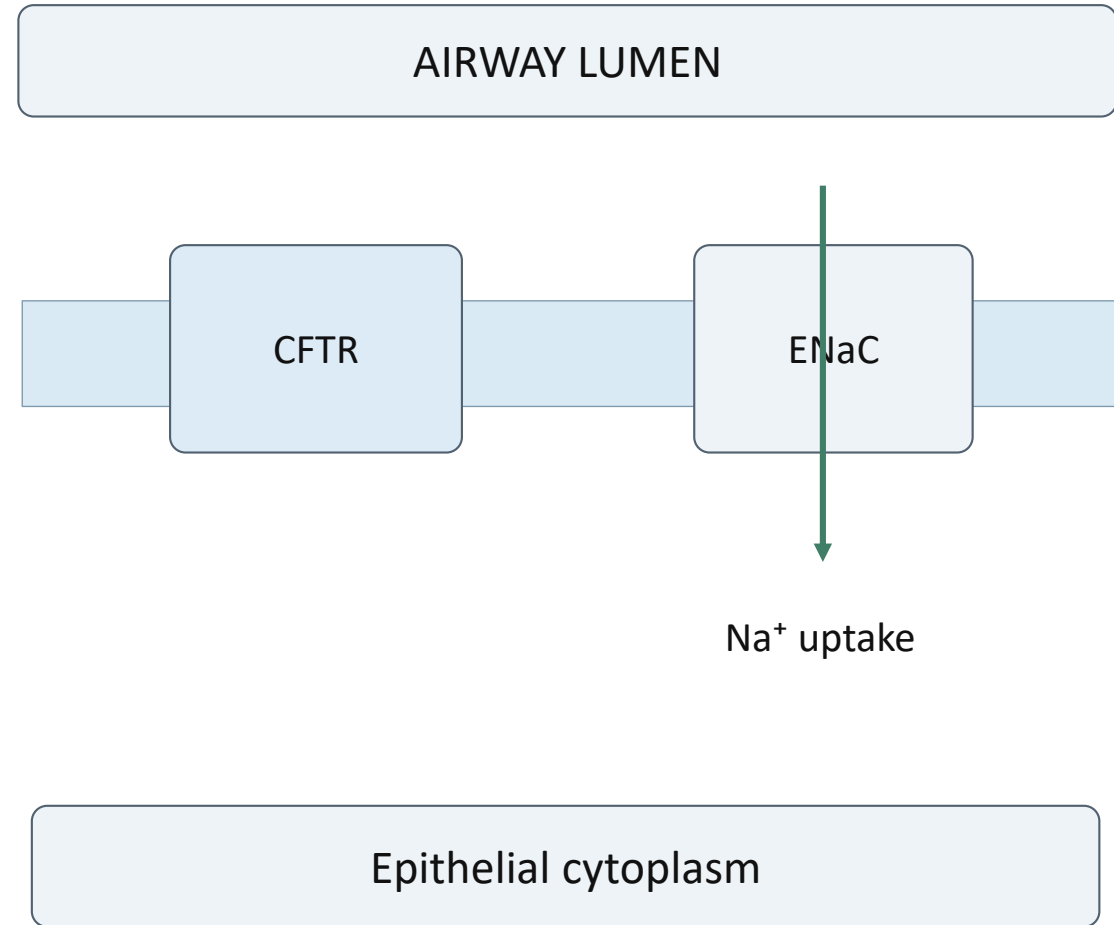
In airway: Restraint

Na⁺ enters cell through ENaC

ENaC direction = lumen → cell

ENaC normally absorbs luminal sodium

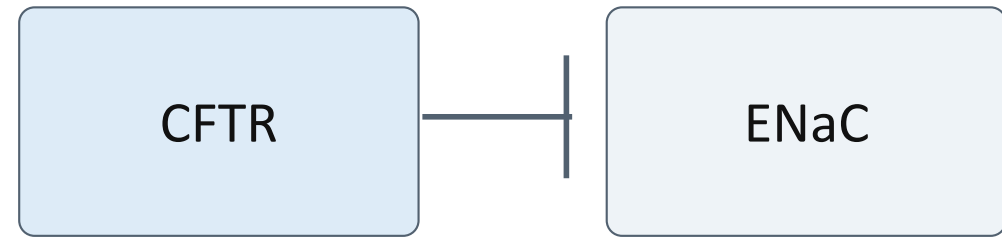
- Sodium moves from the epithelial lumen into cells through ENaC.
- This uptake changes luminal electrolyte balance.
- Sodium transport affects the movement of water across epithelium.



Transport direction is tissue-specific

In the airway, CFTR restrains ENaC activity

- Normal CFTR-mediated inhibition of airway ENaC.
- This restrains sodium uptake from the airway surface liquid.
- Combined with anion secretion, it helps preserve the surface-fluid layer.



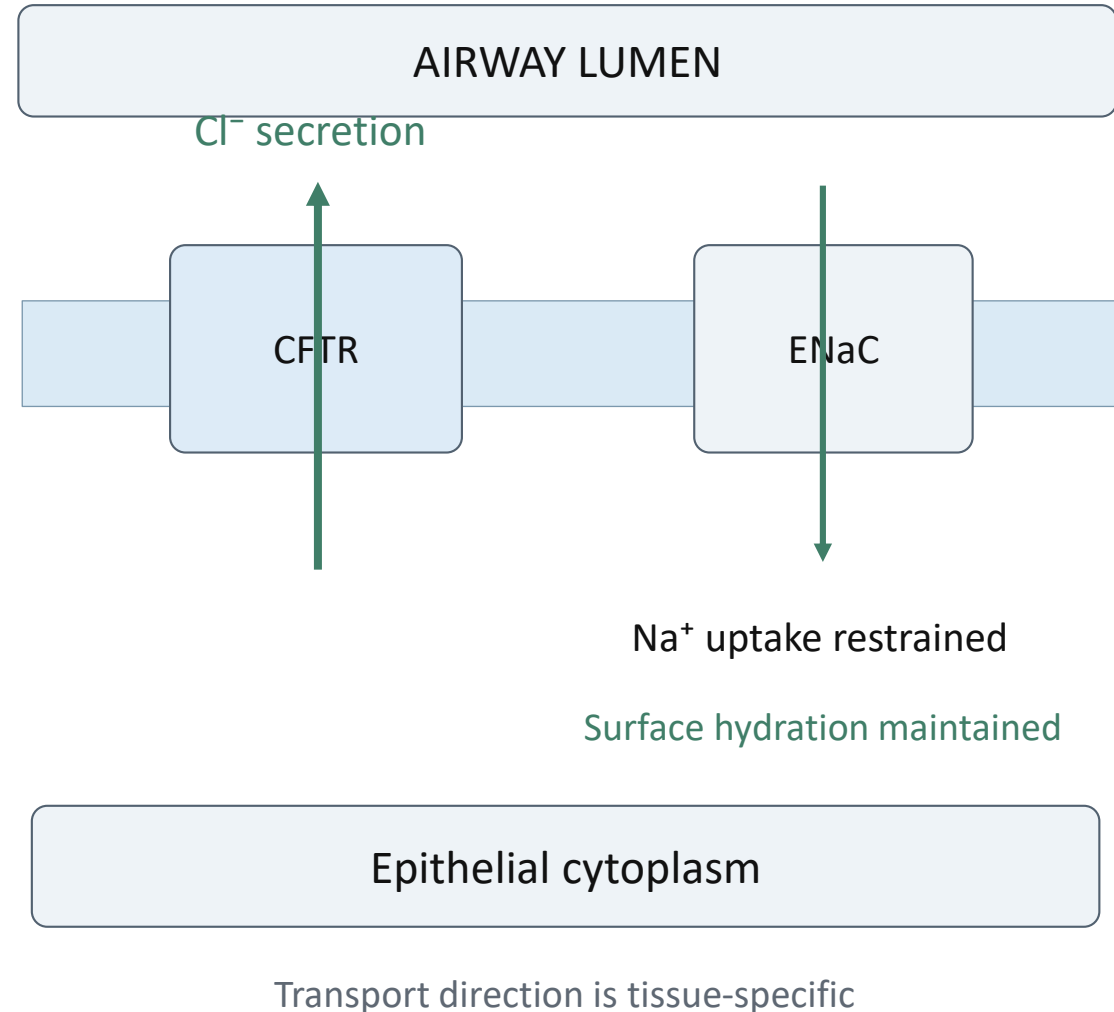
In airway: Restraint

Na⁺ enters cell through ENaC

ENaC direction = lumen → cell

Ion movement governs luminal water volume

- Epithelial ion flux alters osmotic driving forces for water movement.
- Anion secretion helps support luminal fluid.
- Excess sodium reabsorption can favor passive withdrawal of water from the lumen.

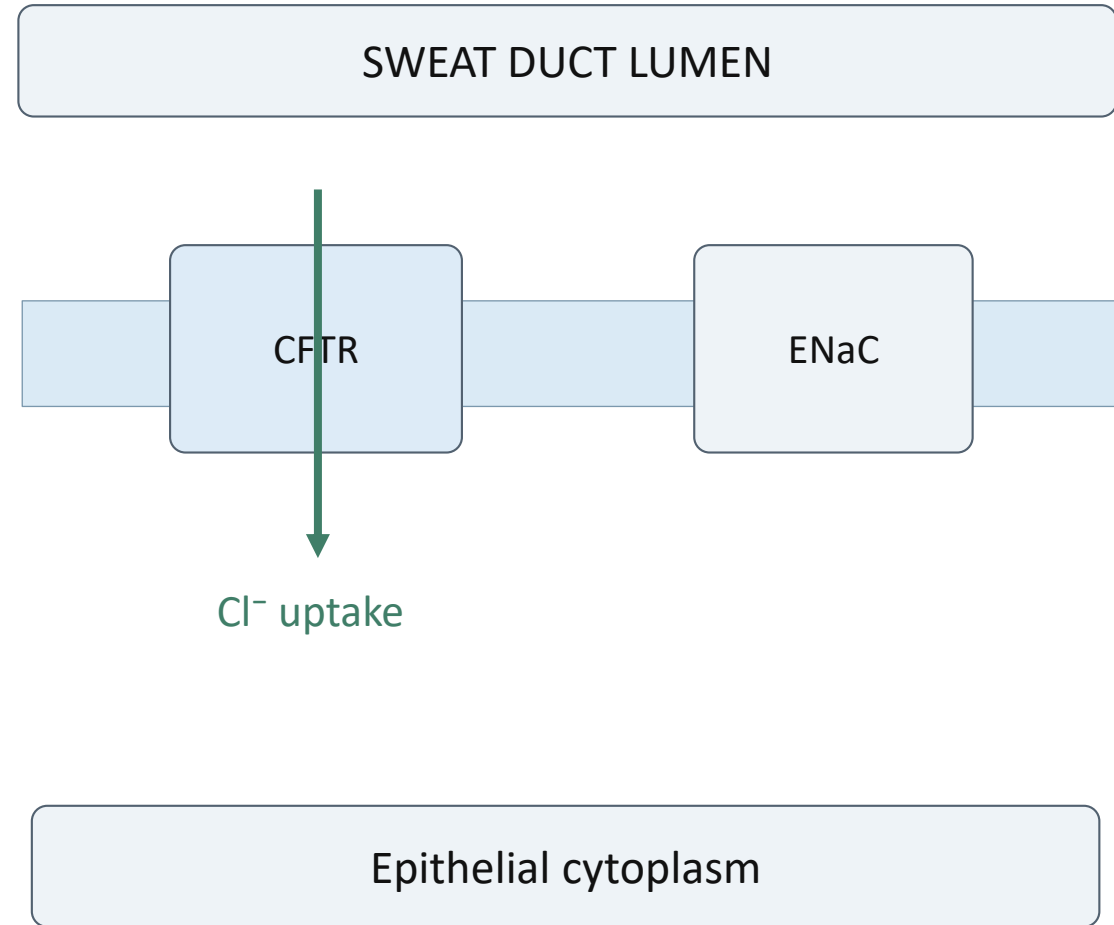


CFTR physiology is explicitly tissue-specific

Tissue	Major normal CFTR role	ENaC relation
Sweat duct	Luminal Cl^- reabsorption	Supports Na^+ reabsorption
Airway	Luminal Cl^- secretion	Restraint of Na^+ uptake
Intestine	Luminal Cl^- secretion	Regulation of luminal fluid

Sweat ducts reclaim chloride from their lumen

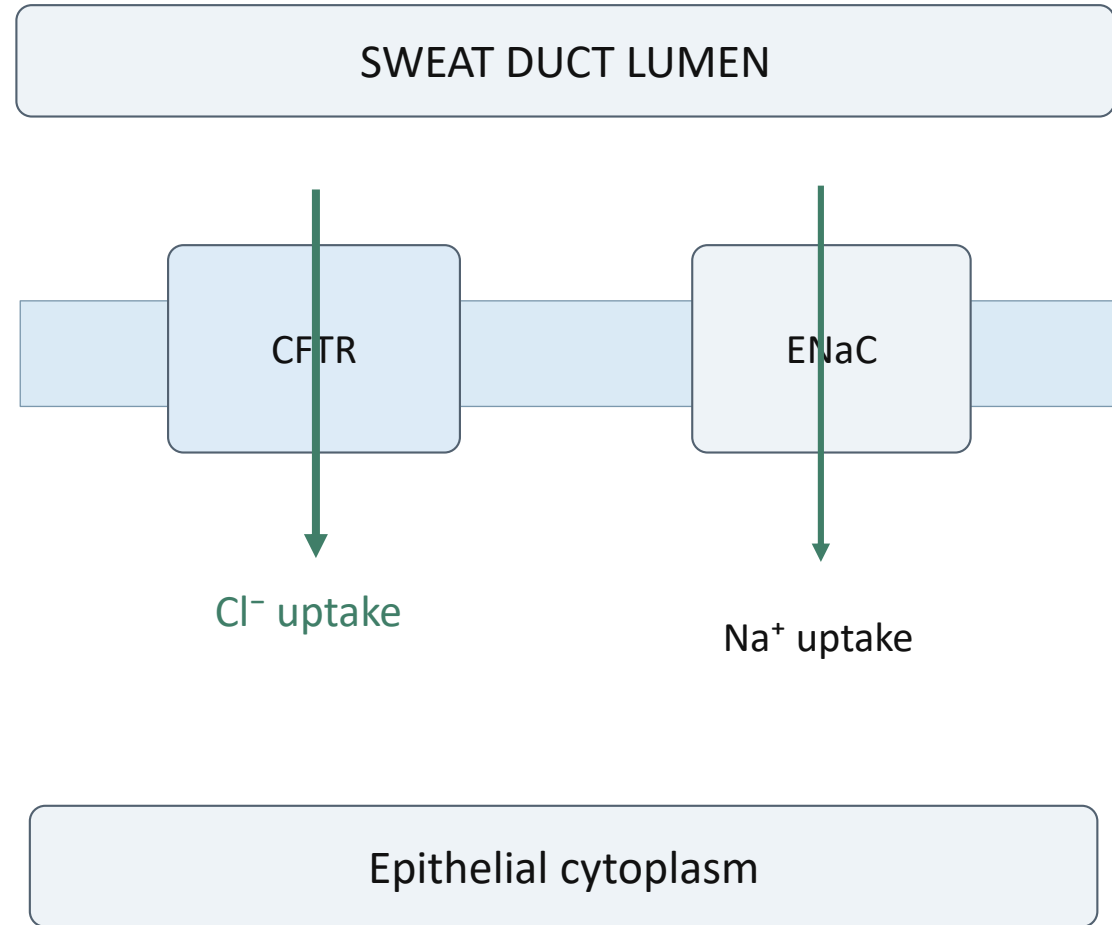
- Ductal CFTR mediates reabsorption of luminal chloride.
- This contrasts with chloride secretion in airways.
- The effect is a reduction in salt remaining in final sweat.



Transport direction is tissue-specific

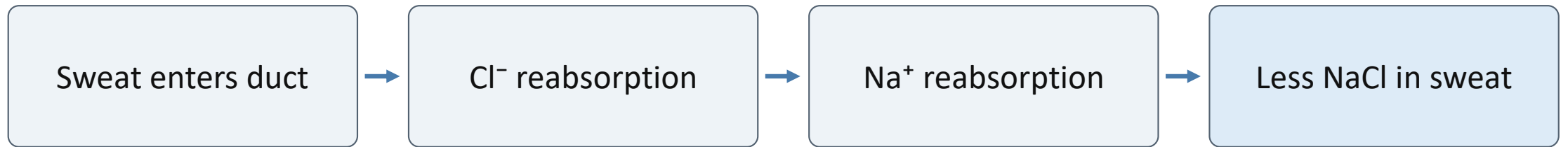
Sweat-duct sodium reabsorption accompanies chloride

- CFTR activity augments ENaC-mediated sodium reabsorption in sweat ducts.
- Na^+ and Cl^- are removed from the duct lumen.
- This supports relatively low salt content of normal sweat.



Transport direction is tissue-specific

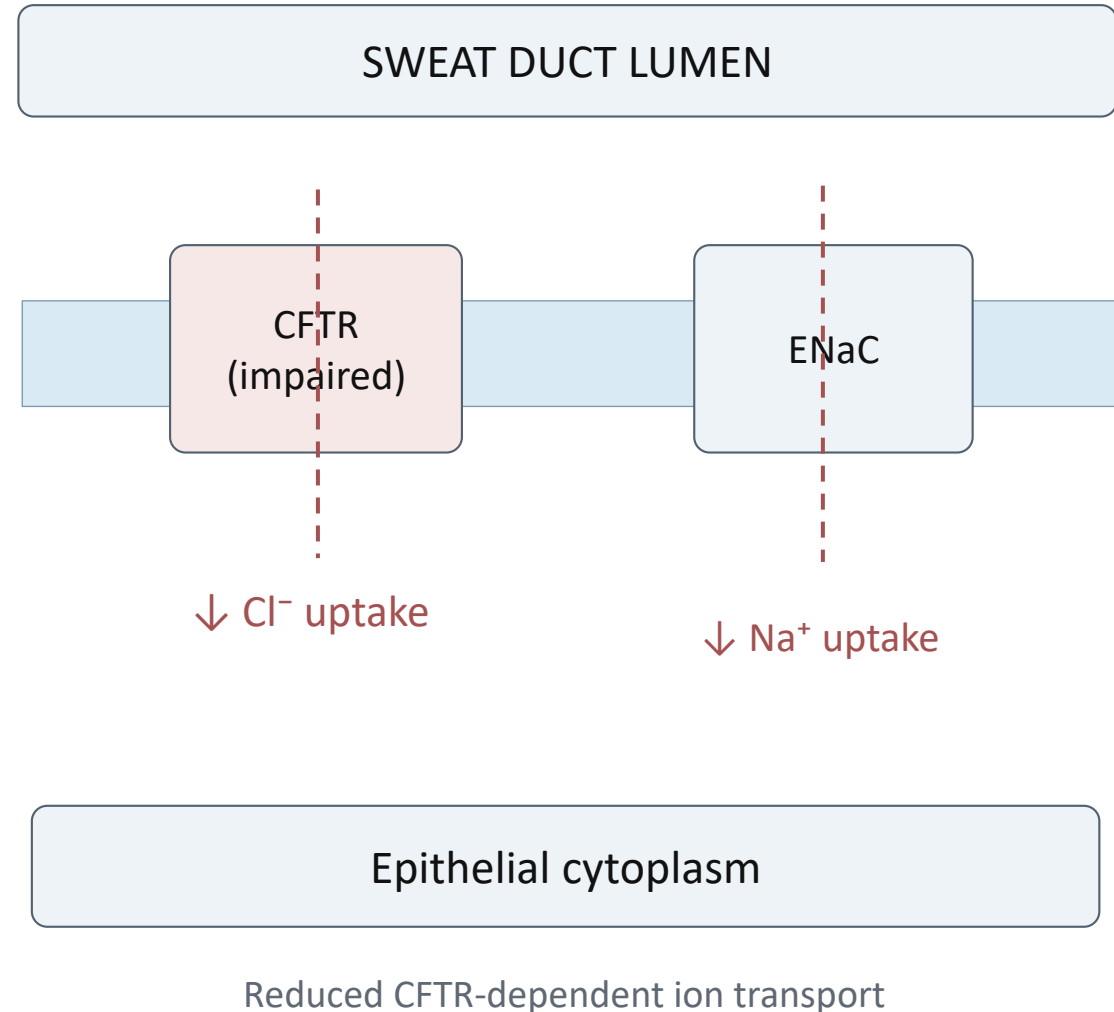
Normal ductal transport reduces final sweat salt



- Sweat duct epithelium reabsorbs salt as fluid passes through the duct.
- CFTR and ENaC support this salt-reabsorptive function.
- The concentration of sodium chloride in secreted sweat therefore falls.

Loss of sweat-duct CFTR impairs salt reclamation

- CFTR dysfunction reduces ductal chloride reabsorption.
- Robbins also describes reduced ENaC activity in the sweat duct.
- More sodium chloride remains in final sweat.

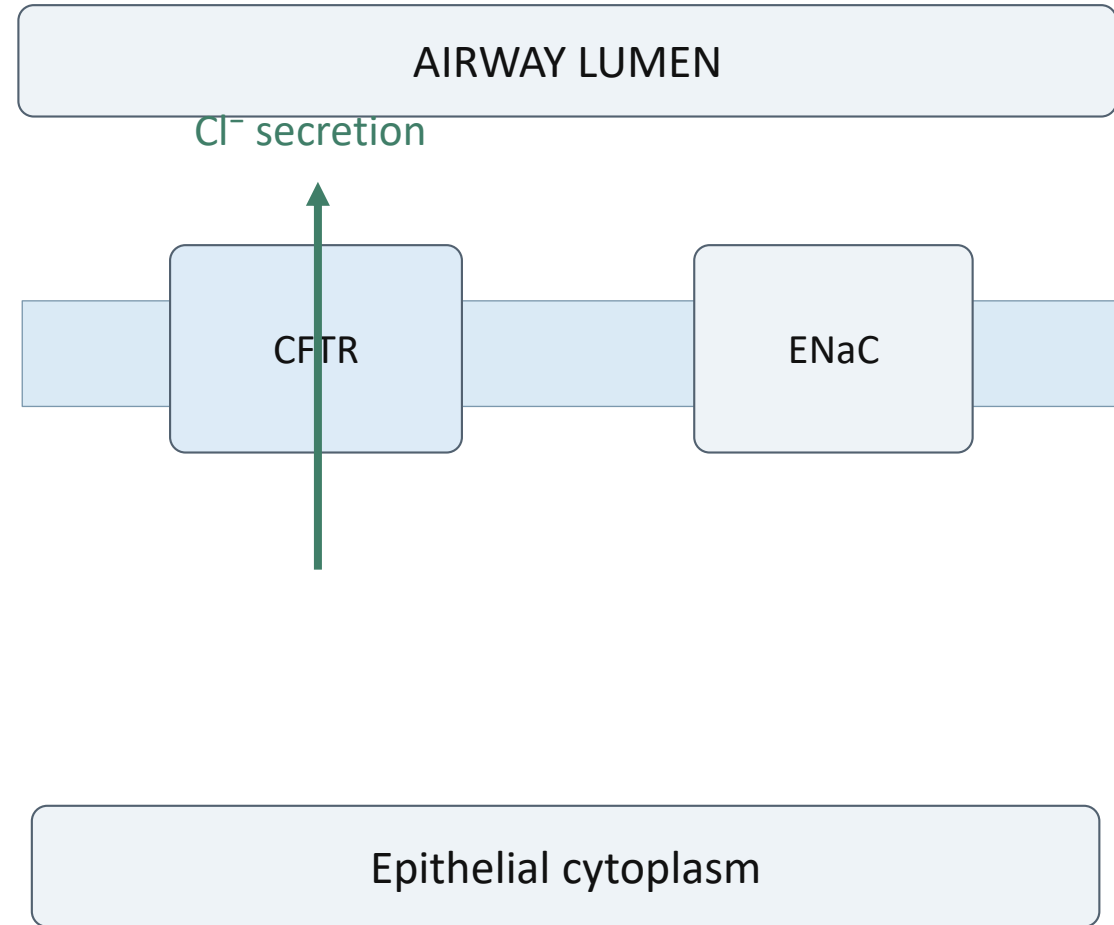


The sweat phenotype follows an absorption defect

Step	Normal sweat duct	CFTR dysfunction
CFTR Cl ⁻ uptake	Effective	Reduced
ENaC Na ⁺ uptake	Augmented	Reduced
Final sweat salt	Lower	Higher

Airway CFTR supports luminal chloride secretion

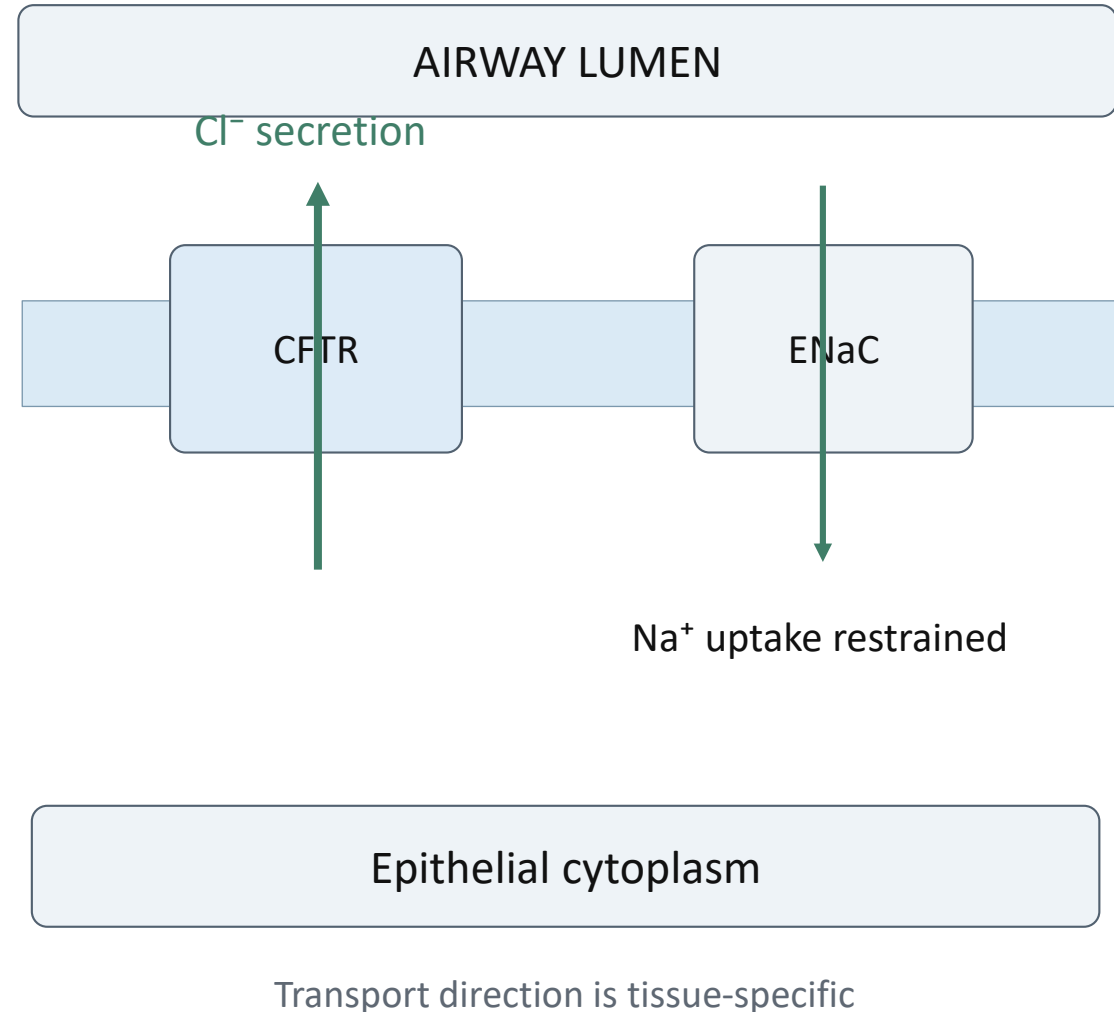
- The airway lumen is outside the apical epithelial surface.
- CFTR transfers chloride toward airway surface liquid.
- This supplies anions to the luminal fluid compartment.



Transport direction is tissue-specific

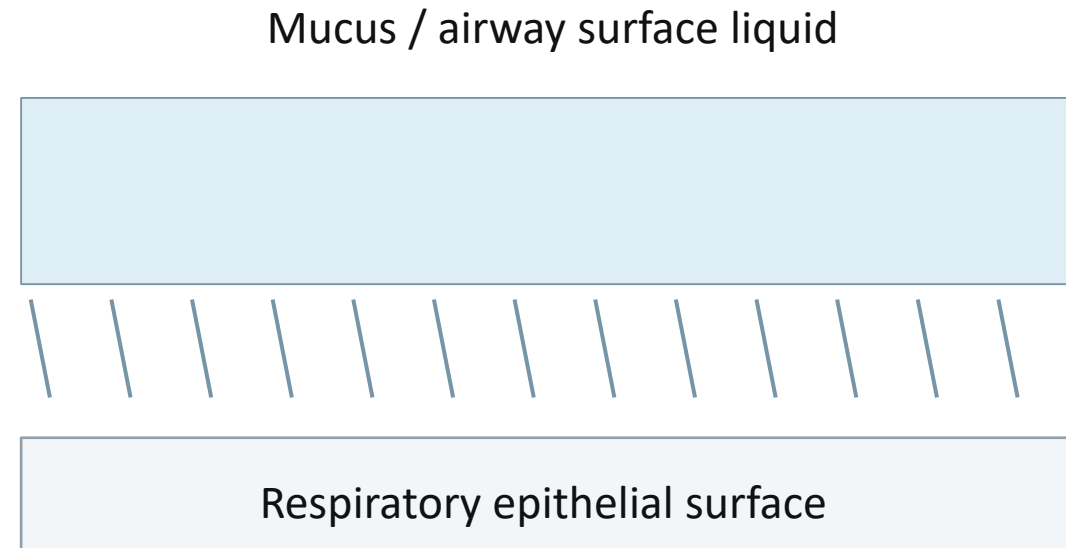
Normal airway transport restrains sodium uptake

- At the airway surface, CFTR inhibits ENaC activity.
- Less luminal sodium is absorbed when the channel network is intact.
- This effect complements CFTR-mediated chloride secretion.



Hydration sustains the airway surface layer

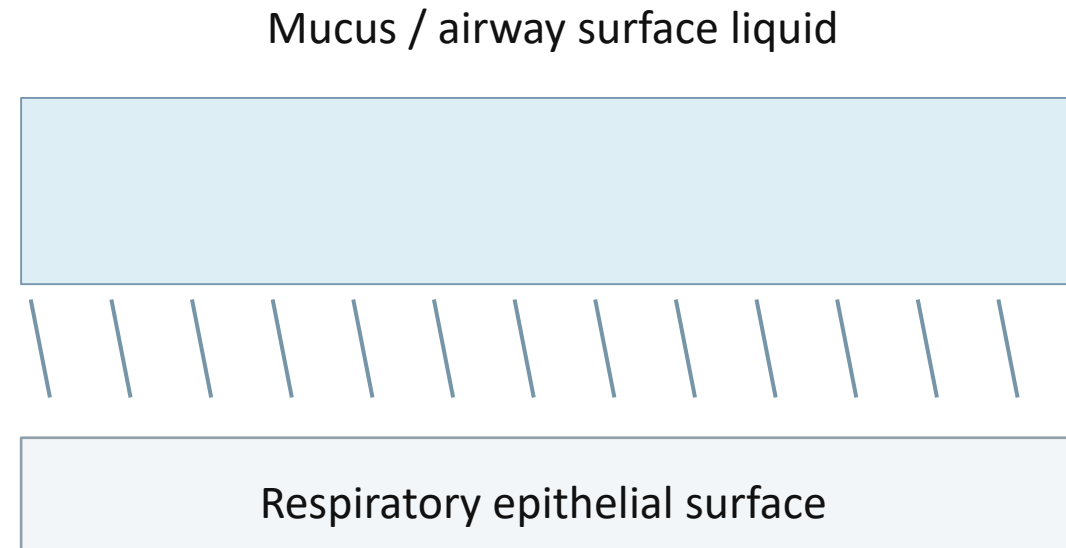
- Surface liquid overlays respiratory epithelial cells.
- Ion transport governs the amount of fluid in that layer.
- Adequate fluid supports movement of the mucus layer.



Hydrated layer permits mucociliary movement

Normal mucus transport requires mucociliary action

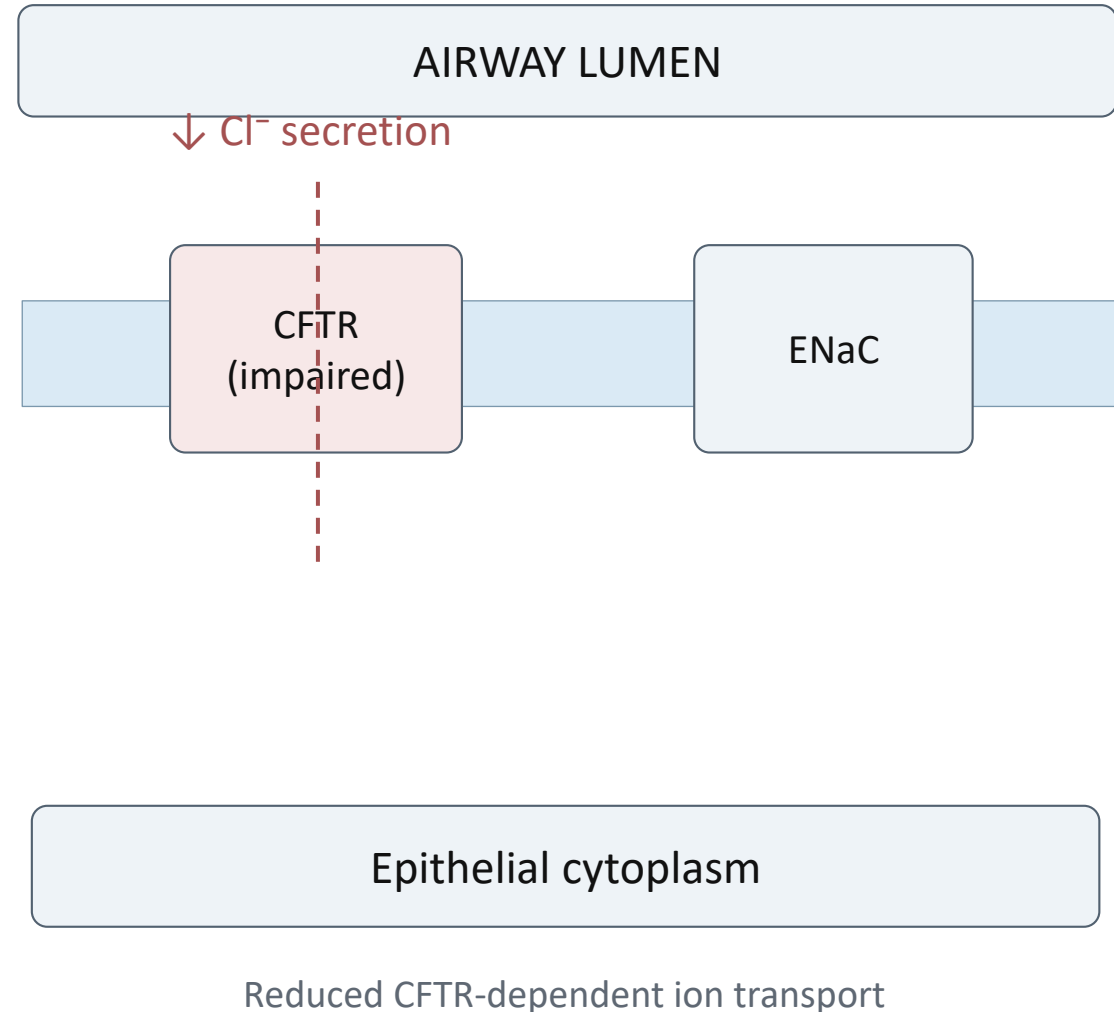
- Mucociliary clearance moves mucus along the airway surface.
- A hydrated surface layer permits this transport.
- The significance of CFTR is therefore functional, not only biochemical.



Hydrated layer permits mucociliary movement

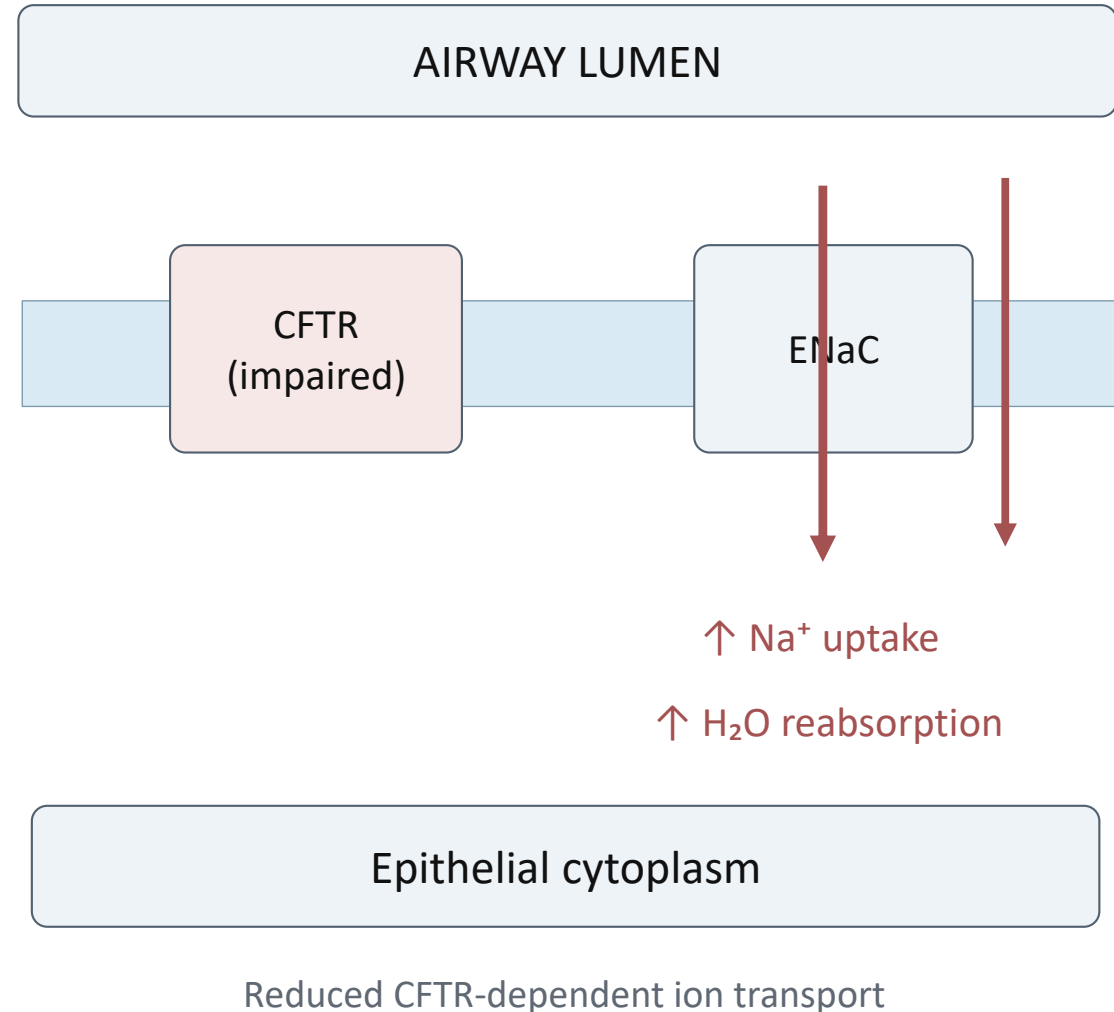
CFTR dysfunction lowers airway chloride secretion

- Impaired CFTR reduces transfer of chloride into the lumen.
- Reduced anion secretion contributes to surface-fluid depletion.
- This differs from the reduction in chloride reabsorption in sweat ducts.



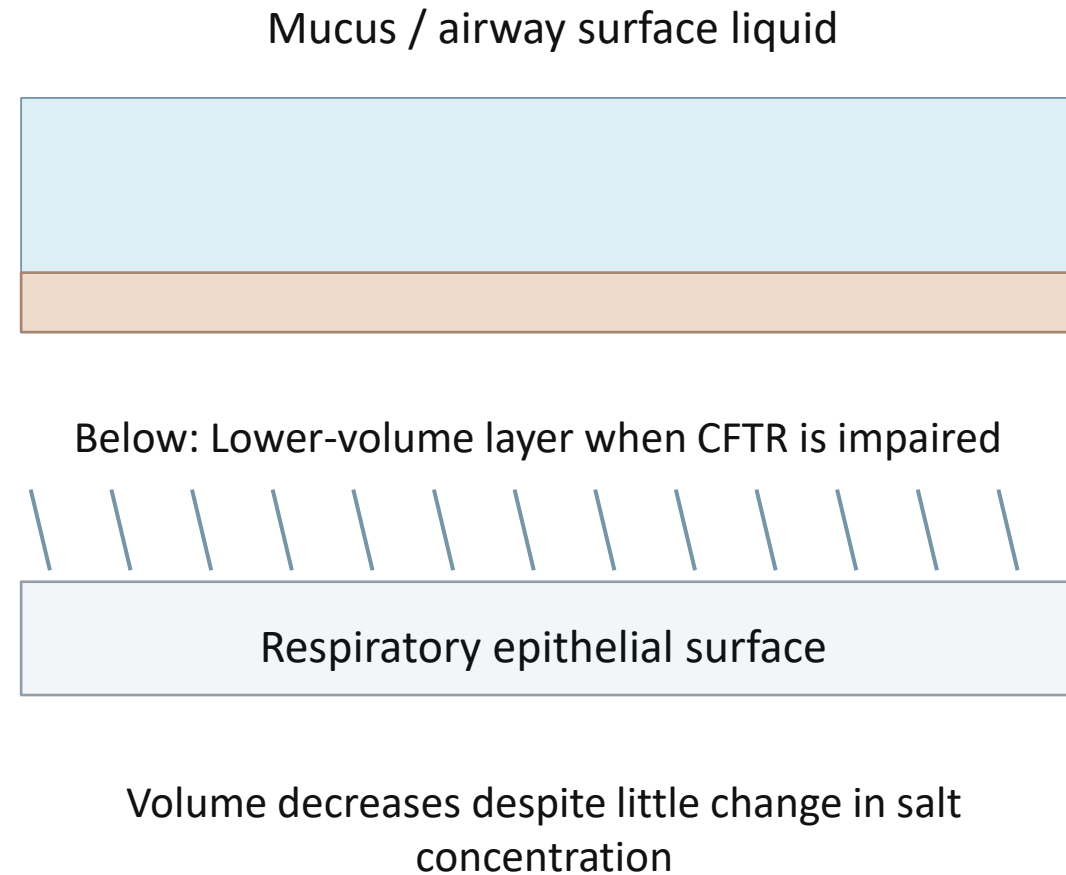
ENaC disinhibition increases airway sodium uptake

- Loss of normal CFTR restraint on airway ENaC.
- Sodium uptake from the lumen increases.
- Water is then more readily reabsorbed from the airway surface layer.



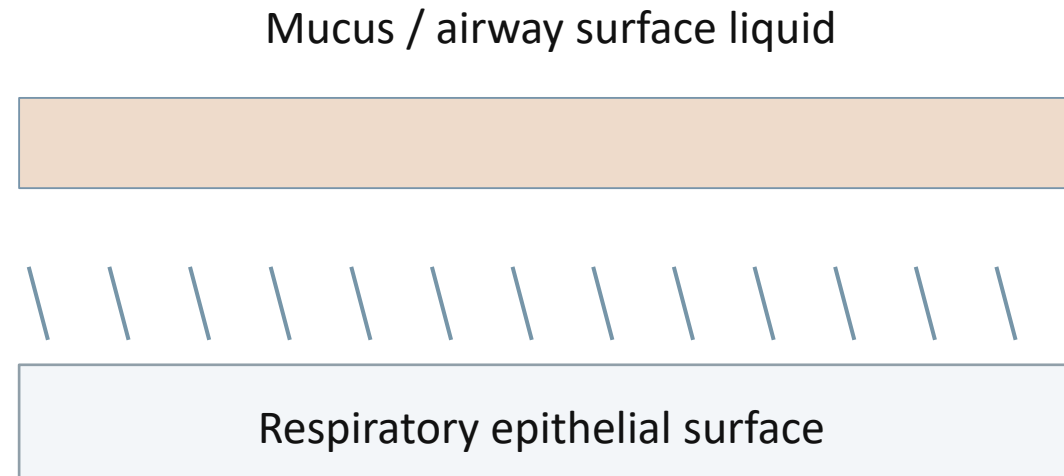
The airway defect primarily reduces fluid volume

- The airway surface liquid becomes depleted in volume.
- An isotonic but low-volume surface layer.
- The principal change is not increased salt concentration of airway surface fluid.



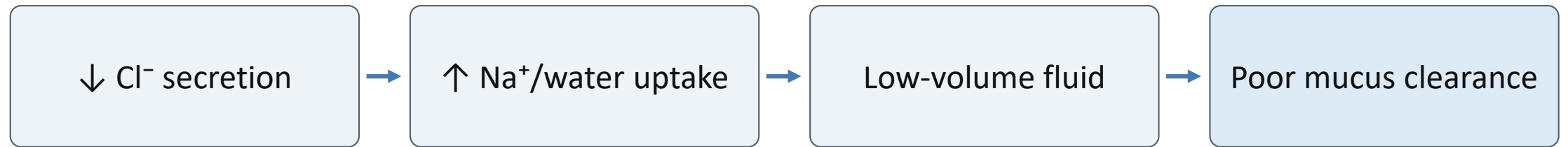
Dehydrated airway mucus becomes concentrated

- Water loss concentrates secreted mucins.
- Mucus becomes viscid and less readily cleared.
- The dense material can obstruct conducting airways.



Concentrated mucus; Clearance impaired

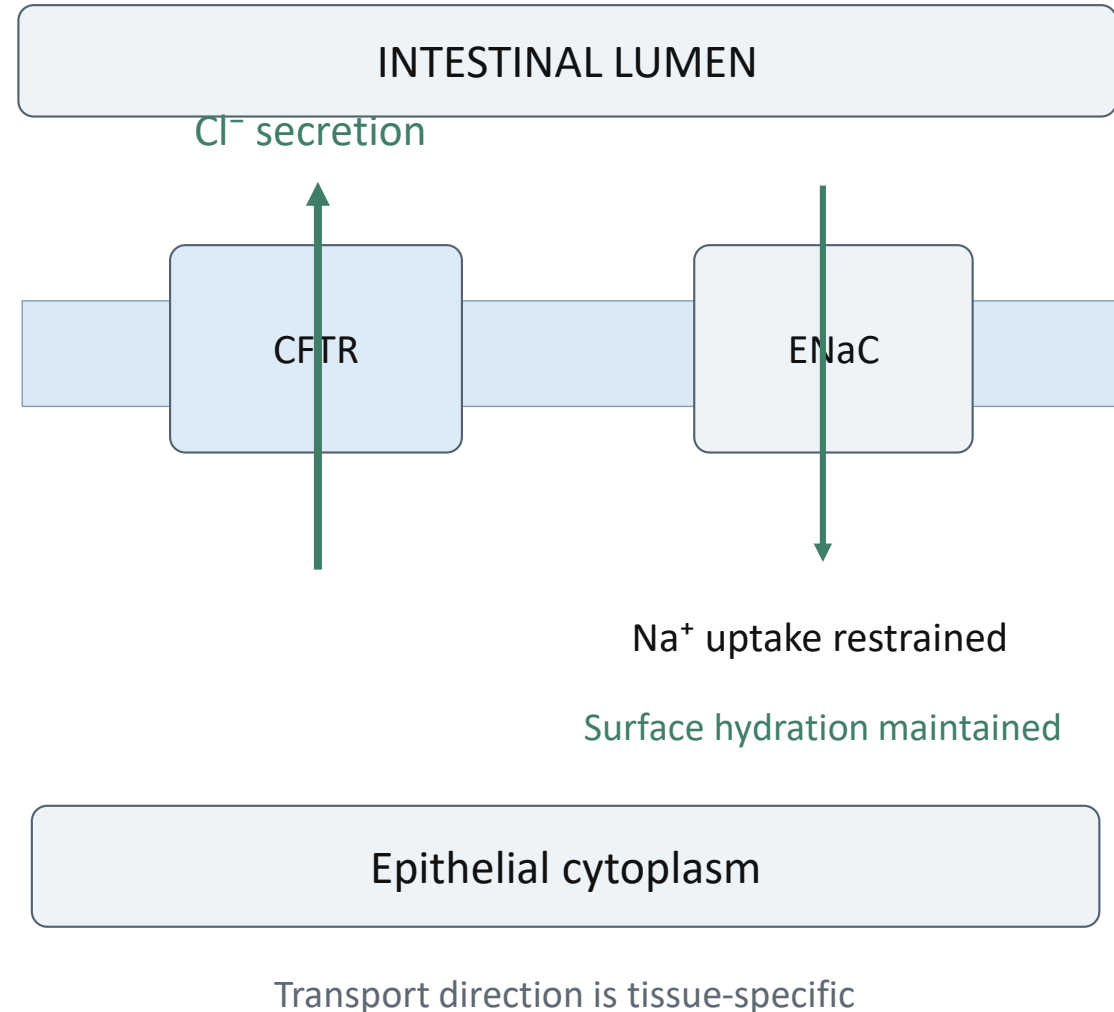
Defective clearance explains downstream risk



- Poor mucociliary transport permits mucus retention.
- Retained secretions facilitate recurrent pulmonary infection.
- These consequences arise downstream of altered epithelial ion transport.

Intestinal CFTR similarly supports secretion

- Intestinal epithelium is another site of luminal chloride secretion.
- The luminal water balance depends partly on epithelial ion distribution.
- Reduced normal CFTR activity favors dehydrated, obstructive secretions.

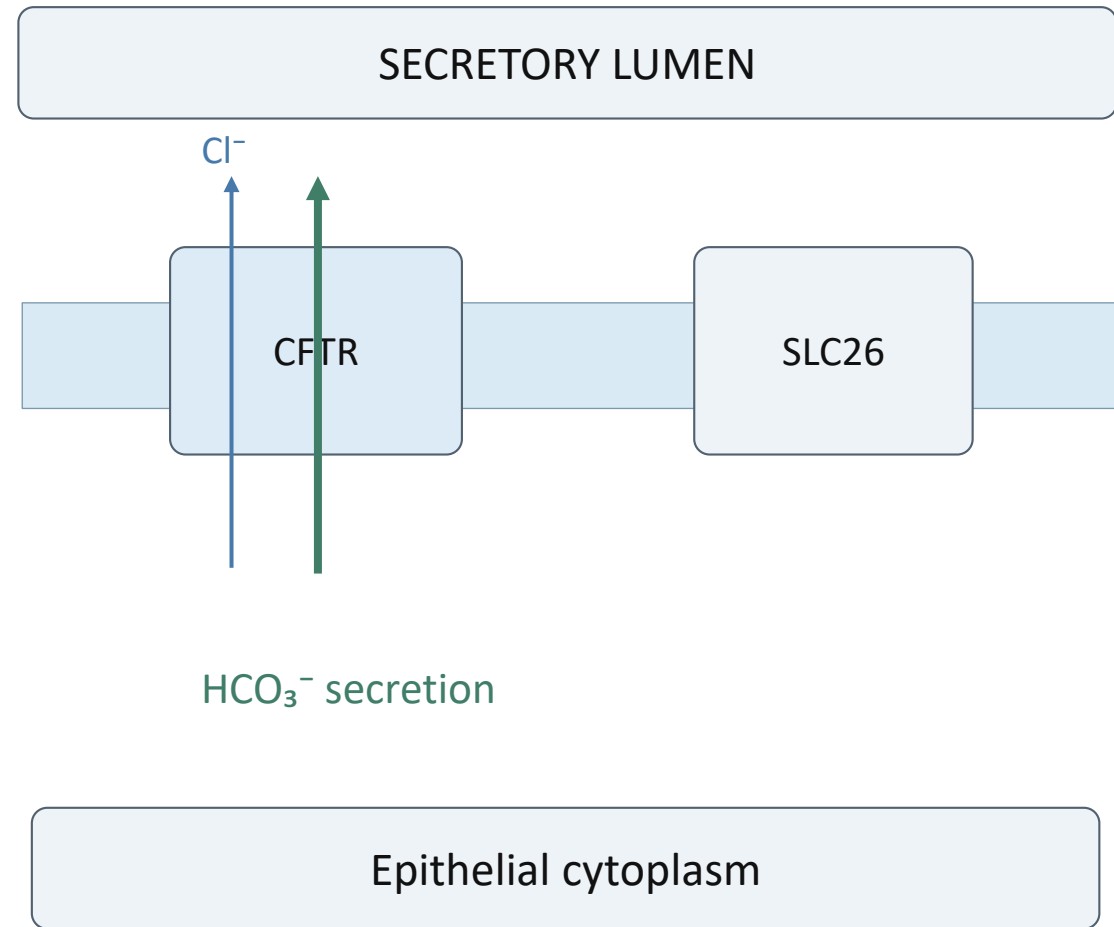


The same mutation can have opposite ion phenotypes

Compartment	Normal CFTR direction	Effect of CFTR loss
Sweat duct	Cl ⁻ lumen → cell	NaCl retention in sweat
Airway	Cl ⁻ cell → lumen	Reduced surface-fluid volume
Intestine	Cl ⁻ cell → lumen	Impaired hydrated secretion

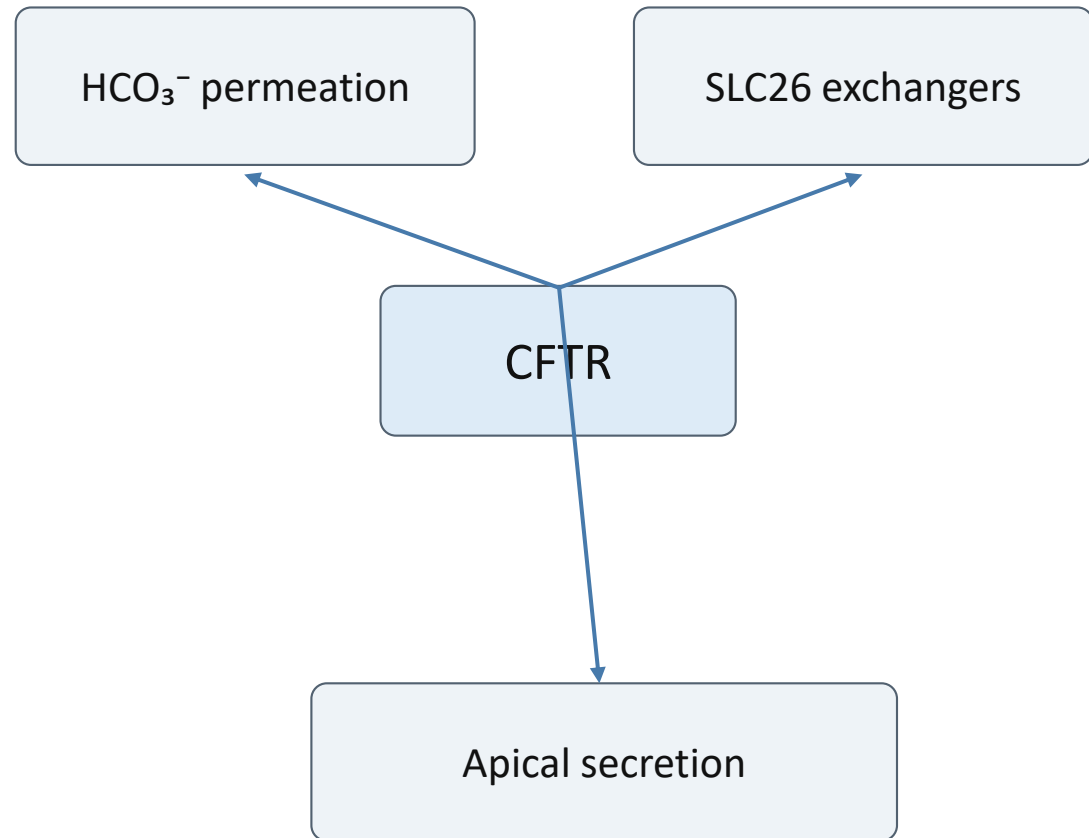
Bicarbonate is a second major CFTR substrate

- The channel directly carries bicarbonate ions.
- Its contribution is not adequately captured by chloride flux alone.
- Bicarbonate transport helps support normal alkaline secretions.

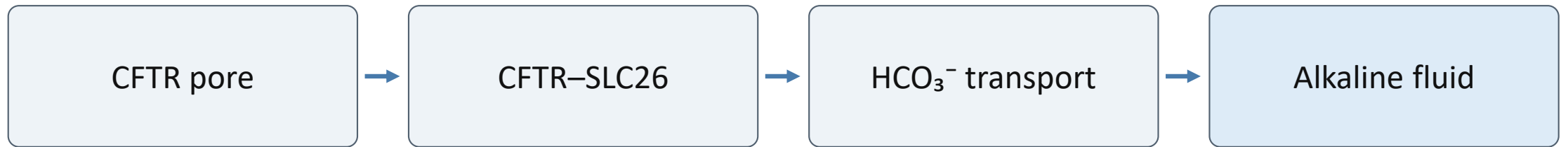


CFTR coordinates with SLC26 exchangers

- SLC26-family anion exchangers are co-expressed at apical surfaces.
- Reciprocal interactions with CFTR.
- This regulatory relationship contributes to epithelial bicarbonate transport.



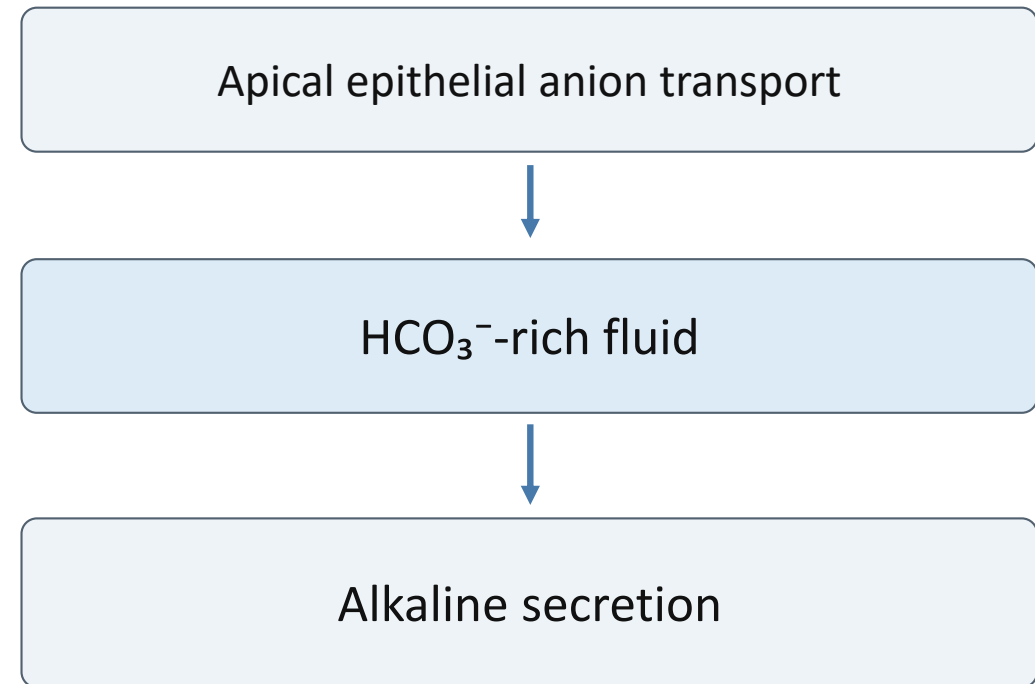
Direct and indirect bicarbonate actions coexist



- CFTR itself conducts HCO₃⁻.
- CFTR also regulates apical SLC26-family anion exchangers.
- Both modes contribute to bicarbonate handling at epithelial surfaces.

Normal bicarbonate secretion produces alkaline fluid

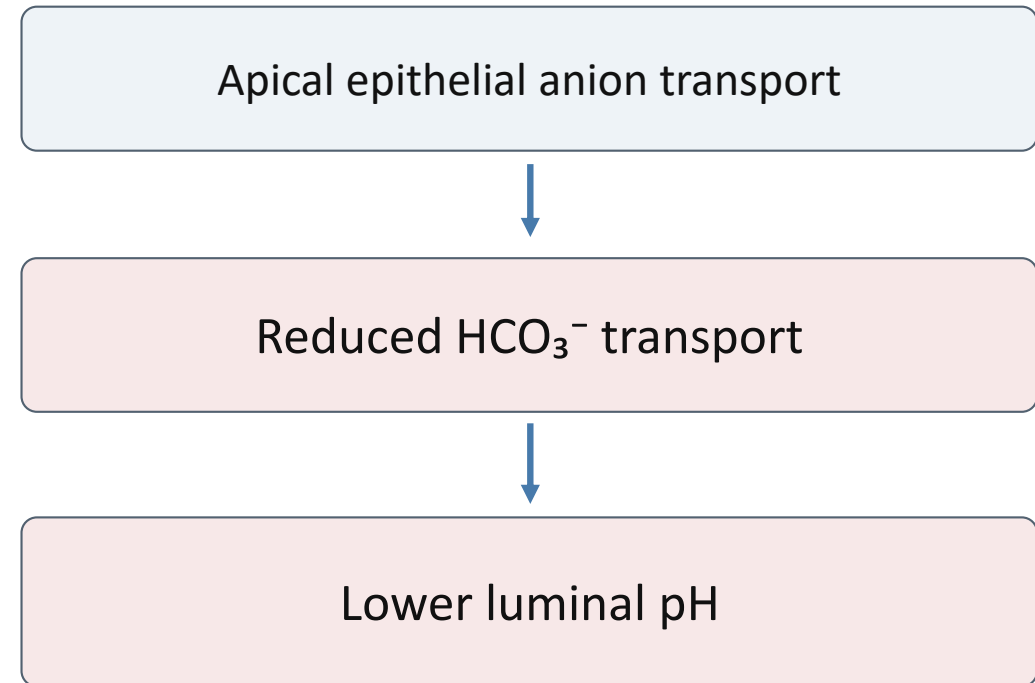
- Bicarbonate supports the luminal pH of epithelial secretions.
- Robbins characterizes normal secretions as alkaline.
- PH is therefore an output of epithelial transport, not merely a laboratory value.



Luminal pH reflects bicarbonate availability

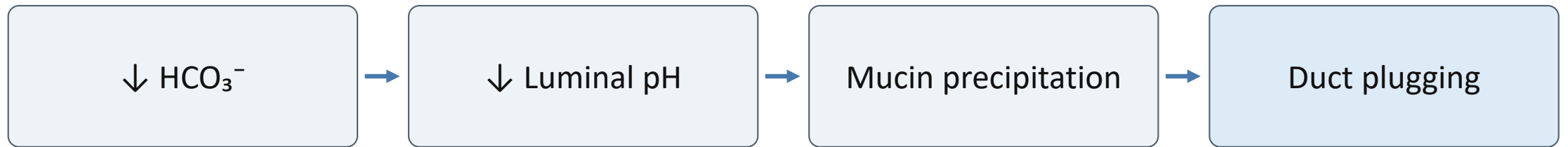
Loss of bicarbonate transport acidifies secretions

- Certain CFTR defects can markedly impair HCO_3^- transport.
- Some of these defects preserve substantial chloride transport.
- The resulting secretion may become abnormally acidic.



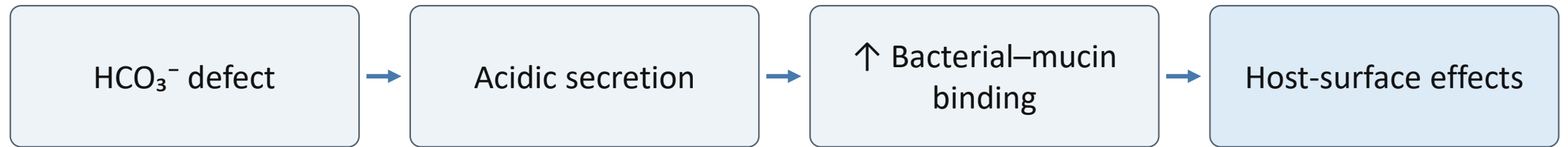
Acidification can alter mucins and duct patency

Lower luminal pH changes mucin behavior



- Reduced bicarbonate lowers luminal pH.
- Acidic secretions to increased mucin precipitation.
- Precipitated mucin can contribute to obstruction of ducts.

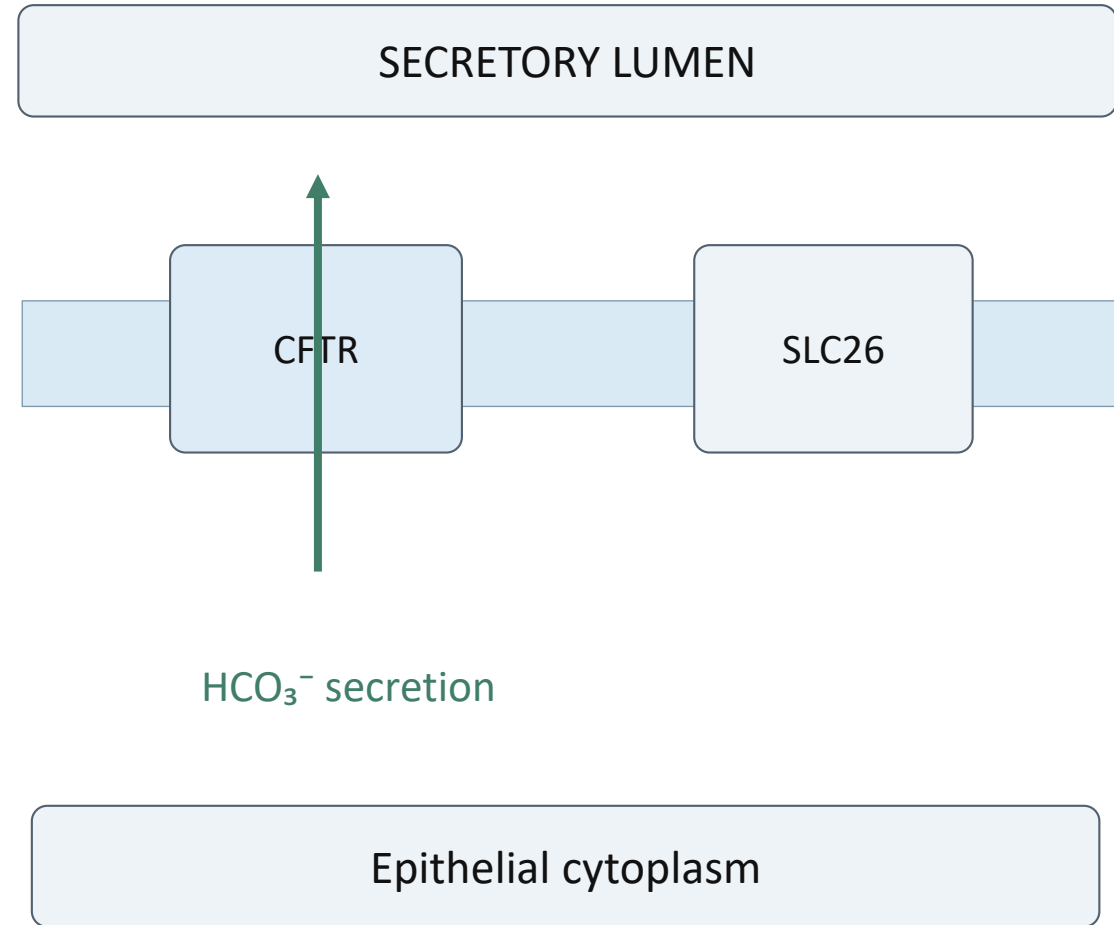
Acidic secretions can favor bacterial binding



- Acidic fluid can increase bacterial binding to mucins.
- This effect is distinct from the low-volume mucus mechanism.
- CFTR transport changes both fluid amount and luminal chemistry.

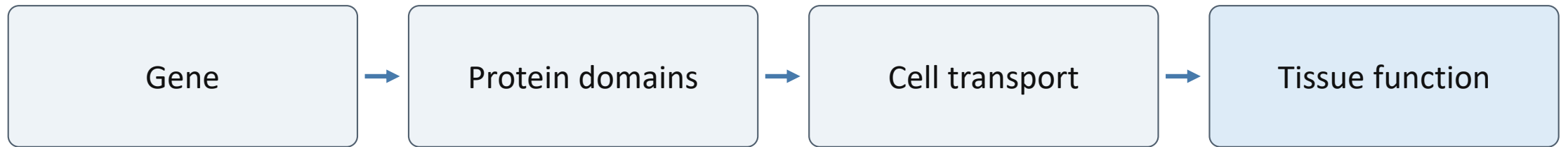
Pancreatic relevance highlights bicarbonate function

- Pancreatic duct secretions depend on bicarbonate transport.
- Marked bicarbonate-conductance defects to pancreatic insufficiency.
- The clinical implication follows from abnormal fluid chemistry and ductal plugging.



Transport direction is tissue-specific

CFTR effects occur at multiple biological scales



- Gene location specifies the encoded protein.
- Domains mediate gating and anion permeation.
- Epithelial polarity and partner channels determine tissue phenotype.

Contrast three CFTR-dependent physiological tasks

Level	Key determinant	Normal output
Molecular	R domain + NBDs	Regulated opening
Sweat duct	CFTR + ENaC uptake	Reduced final NaCl
Airway	Cl ⁻ secretion + ENaC restraint	Hydrated surface liquid
Secretory epithelia	CFTR + SLC26	HCO ₃ ⁻ -rich fluid

Interpretation exercise: Sweat and airway

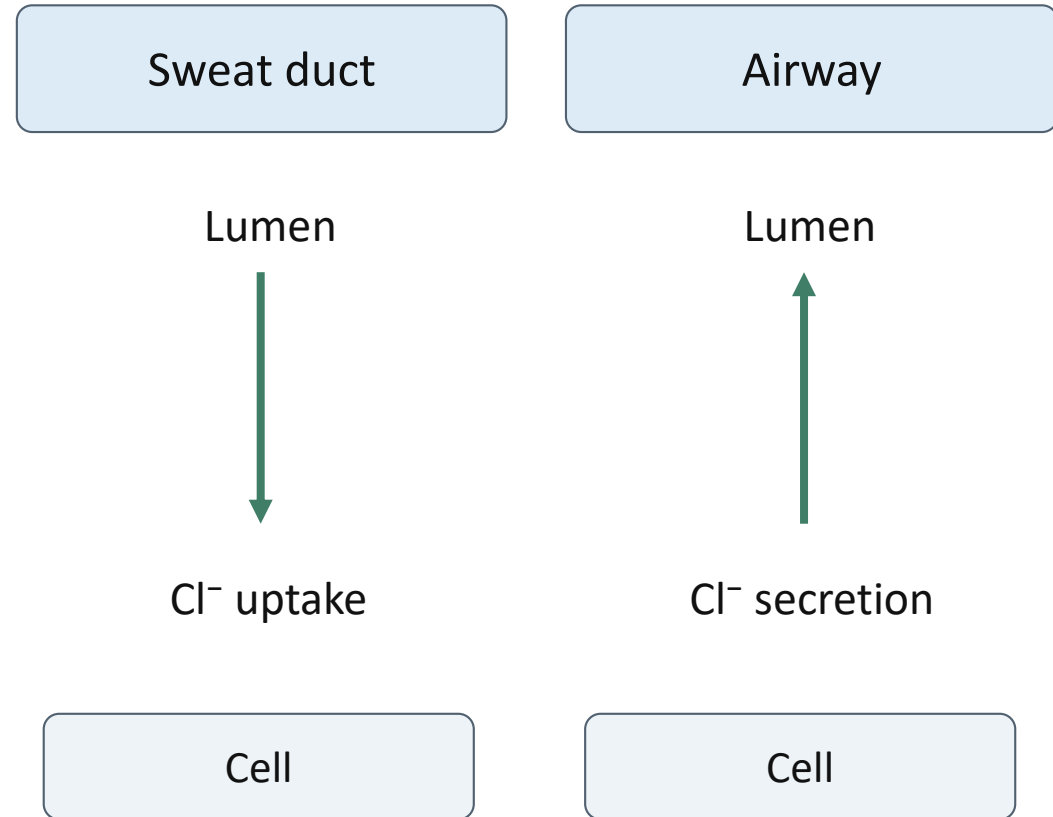
- A defective channel yields salty sweat and dehydrated airway mucus.
- Is the direction of normal chloride transport the same in both tissues?
- Identify the normal direction before considering the disease consequence.

Where does Cl^- normally move?

Reason from the normal physiological mechanism.

Explanation: Different transport directions

- Sweat duct CFTR reabsorbs Cl^- from the lumen.
- Airway CFTR secretes Cl^- into the lumen.
- Both consequences follow from loss of the same protein in different epithelia.



Interpretation exercise: Anion conductance

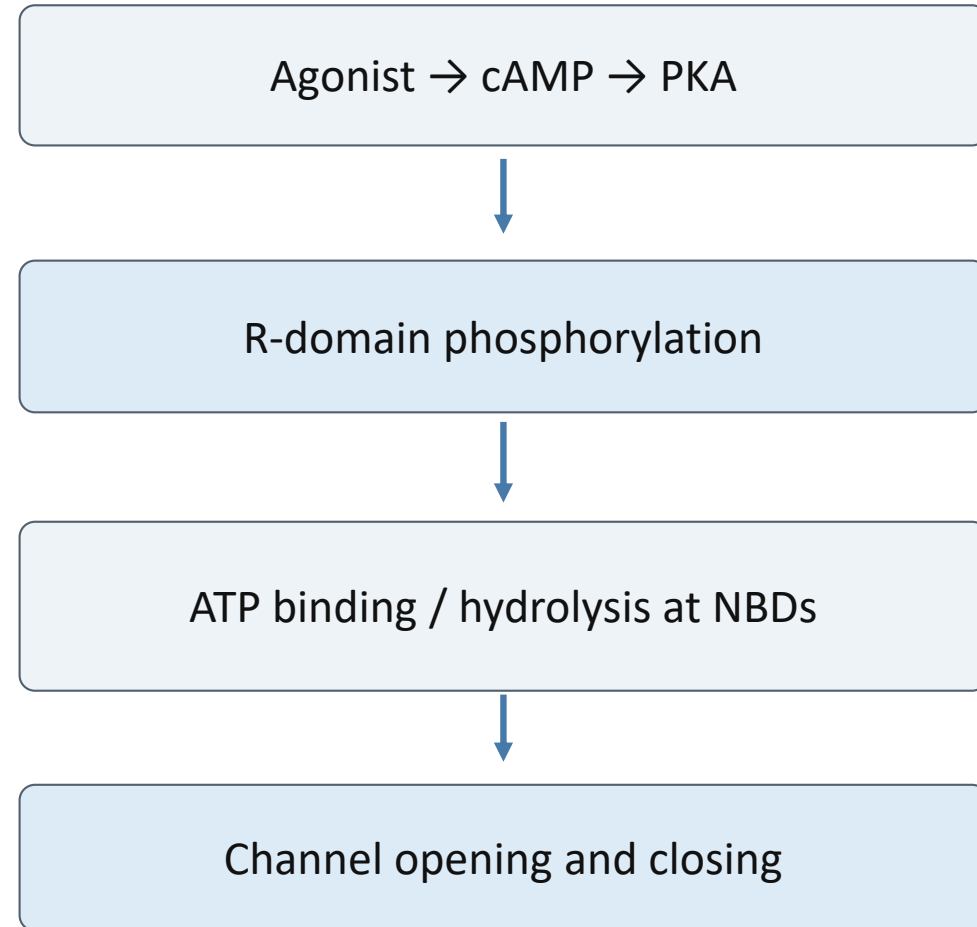
- A hypothetical CFTR protein reaches the apical membrane.
- It has an intact pore but cannot be phosphorylated at its R domain.
- Which step of normal function is directly compromised?

What is most directly affected?

Reason from the normal physiological mechanism.

Explanation: Pore structure is not enough

- TMDs can form the ion pathway without guaranteeing activation.
- R-domain phosphorylation normally supports channel opening.
- ATP-dependent NBD function then couples to gating of the pore.



Five principles to retain

- CFTR is a chromosome 7q31.2–encoded, 1480-residue anion channel.
- Its 2 TMDs, 2 NBDs, and R domain perform distinct tasks.
- CAMP/PKA and ATP regulate chloride and bicarbonate conductance.
- Tissue-specific direction of ion transport explains contrasting effects.

7q31.2 → 1480-aa CFTR

2 TMDs + 2 NBDs + R

CAMP/PKA + ATP gating

Cl⁻ and HCO₃⁻ transport

Primary source and scope

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026).

Chapter 10, pp. 424–426: “Cystic Fibrosis Gene: Normal Structure and Function.”

Conceptual diagrams are original native PowerPoint schematics; no textbook figure was reproduced.