

Surfactant dysfunction disorders

Inherited abnormalities of surfactant transport, secretion and protein function

Genetics • Alveolar pathology • Clinical spectrum

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Learning objectives

- Link surfactant biology to alveolar stability and respiratory failure.
- Compare the ABCA3, SFTPC and SFTPB disease groups.
- Recognize the distinctive light-microscopic, immunohistochemical and ultrastructural findings.
- Distinguish surfactant dysfunction from premature-infant RDS and alveolar proteinosis.

One disease family, several clinical entry points

**Respiratory failure
Soon after birth**

**Progressive disease
In infancy**

**Childhood
Interstitial lung
disease**

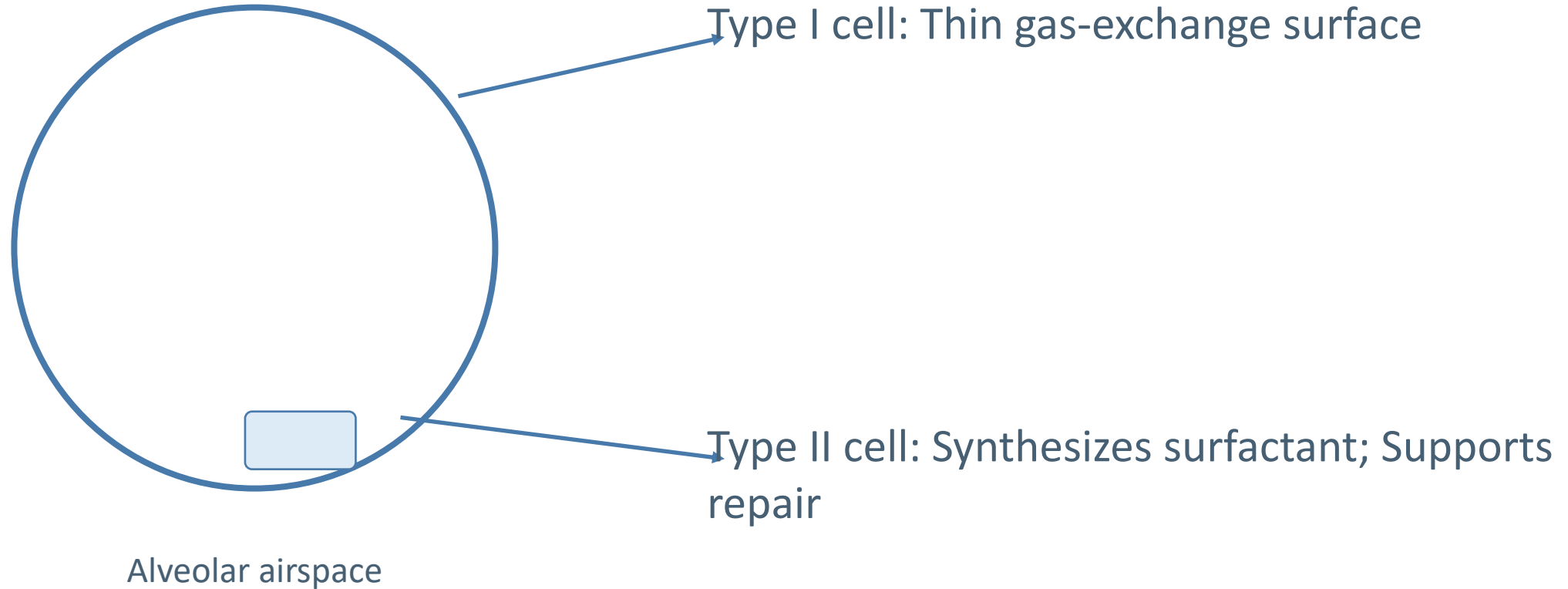
**Adult-onset
Interstitial lung
disease**

Age at presentation is informative, but it does not uniquely identify the gene.

Definition: Inherited disturbance of surfactant handling

- Mutations affect proteins involved in surfactant trafficking or secretion.
- The common target tissue is the alveolar epithelial system.
- The result is a spectrum of alveolar and interstitial lung injury.
- Genetic mechanism is distinct from surfactant accumulation caused by defective macrophage clearance.

The alveolar epithelial unit



Type II pneumocytes are central to these disorders

Normal physiologic roles

- Synthesize alveolar surfactant
- Participate in epithelial repair
- Contain surfactant-related lamellar bodies

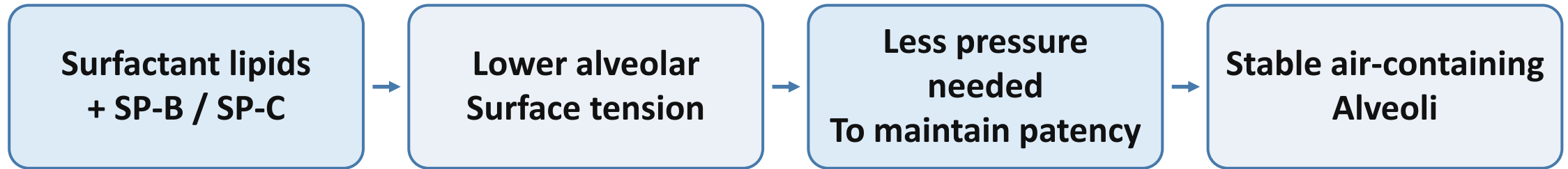
Disease-associated changes

- Abnormal lamellar bodies
- Type II pneumocyte hyperplasia
- Variable alveolar/interstitial injury

Surfactant contains lipids and specialized proteins

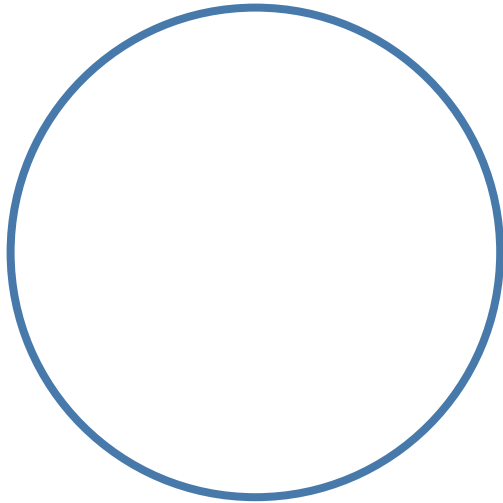
Component	Role stated in Robbins
Dipalmitoyl phosphatidylcholine	Major surfactant phospholipid
Phosphatidylglycerol	Additional phospholipid component
SP-A and SP-D	Hydrophilic proteins contributing to innate host defense
SP-B and SP-C	Hydrophobic proteins supporting reduction of surface tension

Surfactant reduces surface tension at the air–liquid barrier



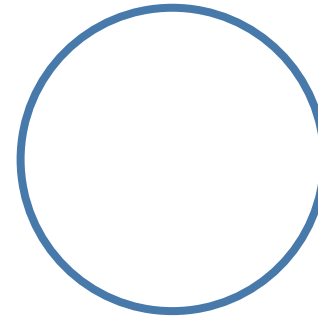
Mechanistic connection: Surface tension determines the work required to reopen alveoli.

Loss of effective surfactant increases work of breathing



Adequate surface activity

Lower opening pressure

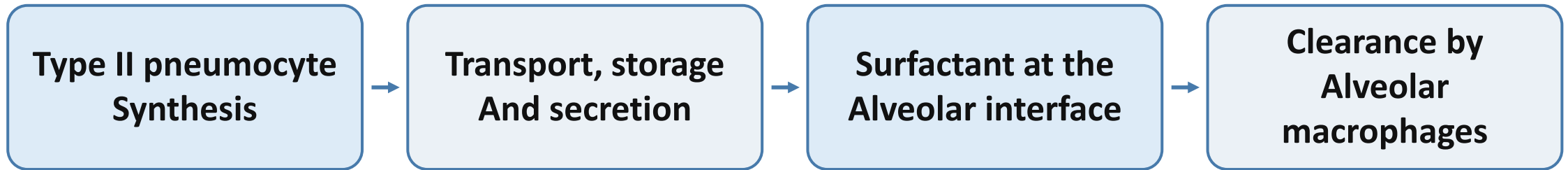


Reduced surface
activity

Repeated collapse; Greater effort

Schematic — depicts physiologic direction, not alveolar measurement

Surfactant homeostasis requires production and clearance



The inherited dysfunctions primarily involve epithelial surfactant handling; PAP primarily involves clearance.

Two mechanistic routes to abnormal surfactant balance

Epithelial surfactant dysfunction

- Mutant surfactant protein or trafficking component
- Abnormal lamellar bodies may develop
- Interstitial and alveolar damage may coexist

Alveolar proteinosis (PAP)

- Impaired macrophage-dependent catabolism
- Surfactant accumulates in airspaces
- Lamellar bodies typically remain normal

Disease mechanisms overlap in airspace material but differ in the primary affected process.

The genotype–phenotype relationship is heterogeneous

- All three gene groups are associated with surfactant dysfunction.
- The most severe disease may present as early respiratory failure.
- A chronic interstitial lung disease phenotype can be recognized later in life.
- Age, microscopic appearance and a family history provide clues rather than a unique genotype.

Principal genes in the Robbins account

Gene / protein	Relative frequency	Inheritance
ABCA3	Most commonly mutated	Autosomal recessive
SFTPC / surfactant protein C	Second most common	Autosomal dominant
SFTPB / surfactant protein B	Third most common	Autosomal recessive

Frequency is a textbook ranking, not a population-specific estimate.

Each gene disrupts the surfactant system differently

ABCA3
Lipid transport

SFTPC
Protein C pathway

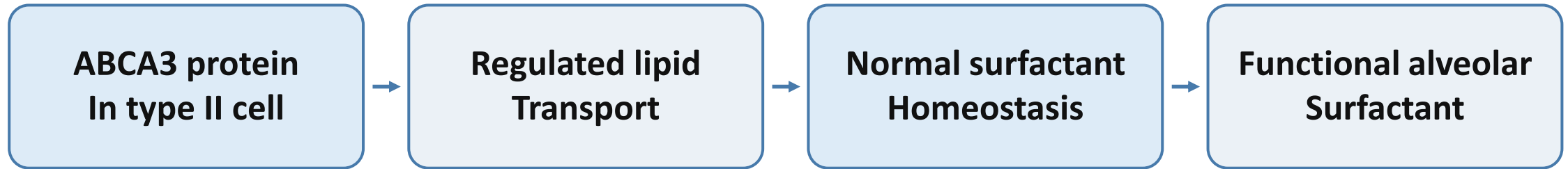
SFTPB
Protein B pathway

Different molecular starting points converge on abnormal alveolar surfactant biology.

ABCA3: Membrane-associated lipid transport

- ABCA3 encodes an ATP-binding cassette transporter.
- The protein is transmembrane and participates in lipid transport.
- Its activity contributes to surfactant homeostasis.
- Loss of normal function is associated with abnormal type II-cell lamellar bodies.

ABCA3 links lipid trafficking to lamellar-body biology



Disruption of the transporter is associated with an abnormal lamellar-body ultrastructure.

ABCA3-associated disease is autosomal recessive

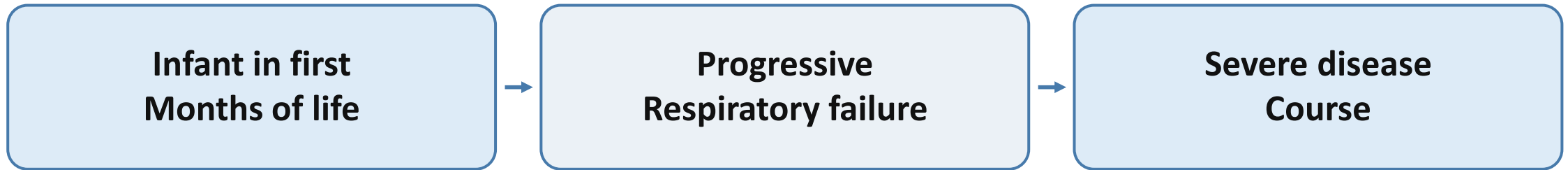
Inheritance pattern

- Autosomal recessive transmission
- Both gene copies are relevant to the affected genotype
- A pedigree can support, but not replace, molecular evaluation

Pathologic association

- Altered surfactant homeostasis
- Abnormal lamellar-body ultrastructure
- Variable alveolar and interstitial changes

ABCA3: The typical early-life phenotype



Rapidly progressive respiratory failure with a frequently fatal outcome in this presentation.

ABCA3: Disease may present beyond infancy

- A minority of affected patients first come to attention in older childhood or adulthood.
- The later phenotype is often a chronic interstitial lung disease.
- An adult presentation does not exclude an inherited surfactant disorder.
- The section provides no reliable prevalence or age-specific penetrance estimates.

ABCA3 has a broad clinical spectrum

More typical clinical pattern

- Presentation in the first few months
- Rapidly progressive respiratory failure
- Severe prognosis account

Less common clinical pattern

- Recognition in older children or adults
- Chronic interstitial lung disease
- Severity cannot be inferred from age alone

SFTPC encodes surfactant protein C

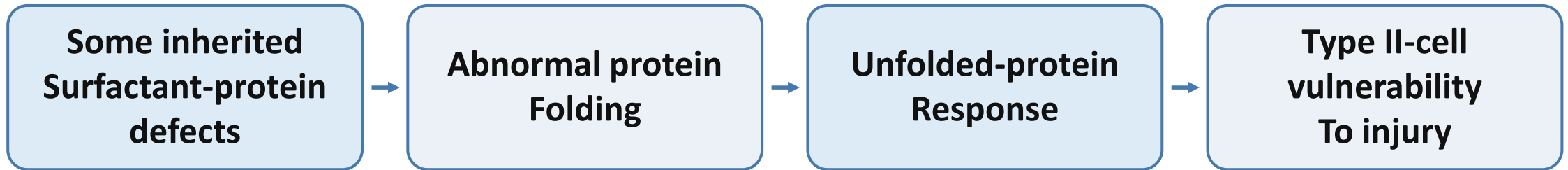
- SP-C belongs to the hydrophobic surfactant protein group.
- Together with surfactant lipids, it helps reduce alveolar surface tension.
- SFTPC is the second most commonly mutated gene in the source section.
- The disorder follows an autosomal dominant inheritance pattern.

SFTPC: Dominant inheritance and variable course



The textbook does not provide one obligatory age of onset or disease trajectory for SFTPC-associated disease.

Surfactant-protein misfolding can injure type II cells



Related Robbins context: This mechanism is described for rare familial interstitial fibrosis.

SFTPC: Interpretation requires phenotype awareness

- The clinical course may be highly variable between affected individuals.
- Neither severe neonatal disease nor adult interstitial disease is obligatory.
- Protein C deficiency is one of the conditions with potentially informative IHC findings.
- A histologic pattern alone does not establish a specific SFTPC mutation.

SFTPb encodes the surface-active protein B

- SP-B is a hydrophobic surfactant protein.
- It cooperates with the lipid layer to reduce air–liquid surface tension.
- SFTPb is the third most commonly mutated gene in this source section.
- The associated disorder has autosomal recessive inheritance.

SFTPB deficiency may present in a full-term infant



A severe neonatal surfactant phenotype is not confined to prematurity.

SFTPb deficiency: Prognosis

- The typical reported phenotype has relentless early respiratory distress.
- Death between 3 and 6 months without lung transplantation.
- The prognosis described applies to the typical severe deficiency phenotype.
- No genotype-specific treatment-response rates are stated in this source section.

Severe genetic dysfunction differs from simple immaturity

Prematurity-related RDS

- Surfactant deficiency from pulmonary immaturity
- Strong relationship with gestational age
- Lung maturation and exogenous surfactant are central in source discussion

Inherited SFTPb deficiency

- May affect a full-term newborn
- Autosomal recessive protein deficiency
- Severe course can persist despite the absence of prematurity

Comparative clinical profiles of the three genes

Gene	Typical source-described presentation	Important exception / course
ABCA3	First months: rapidly progressive respiratory failure	Later childhood or adult ILD possible
SFTPC	Variable timing and severity	Highly variable clinical course
SFTPB	Full-term neonate: distress soon after birth	Severe course; transplant mentioned

Clinical onset alone is not a molecular diagnosis

Useful clinical clues

- Full-term severe neonatal respiratory distress
- A family history compatible with dominant disease
- Chronic ILD in an older child or adult

Limits of inference

- Overlapping phenotypes across genetic groups
- A variable course can occur within a gene group
- Microscopy and protein findings require correlation

Histology: A mixed alveolar and interstitial pattern

**Intraalveolar
Granular material**

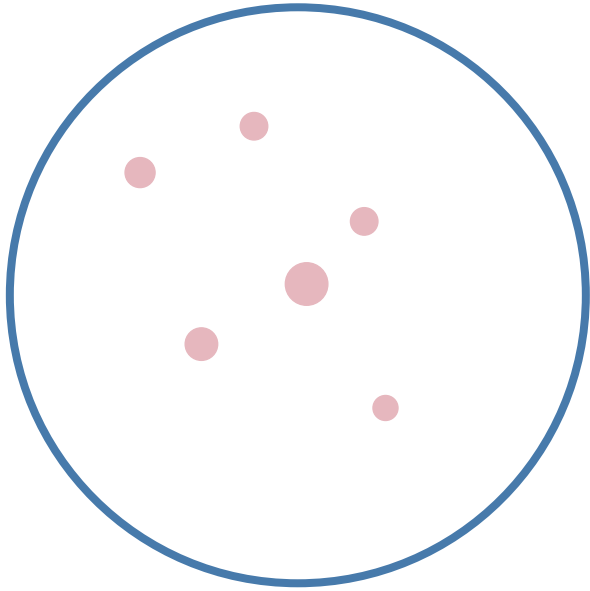
**Type II pneumocyte
Hyperplasia**

**Interstitial
Fibrosis**

**Alveolar
Simplification**

These findings occur in variable amounts; They are not four universal obligatory criteria.

Intraalveolar material is pink and granular

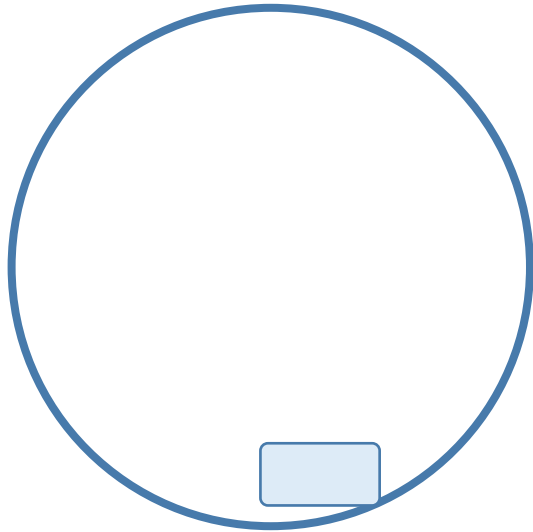


Granular airspace deposits

Schematic — not an H&E image

- The intraalveolar material is eosinophilic on routine histology.
- Amounts vary between cases.
- Airspace material alone does not distinguish genetic disease from PAP.

Type II pneumocyte hyperplasia reflects epithelial response

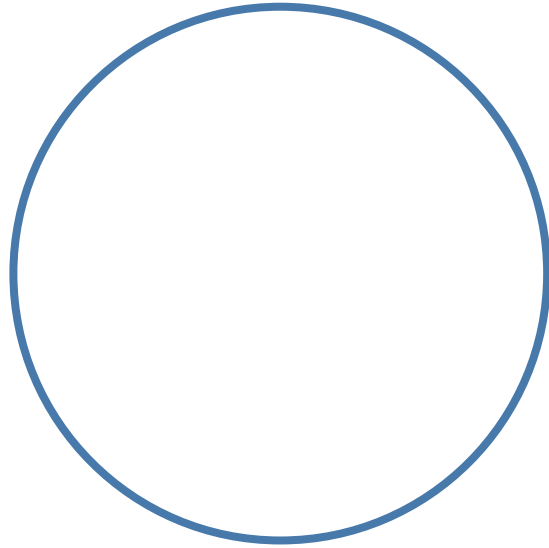


Type II epithelial
compartment

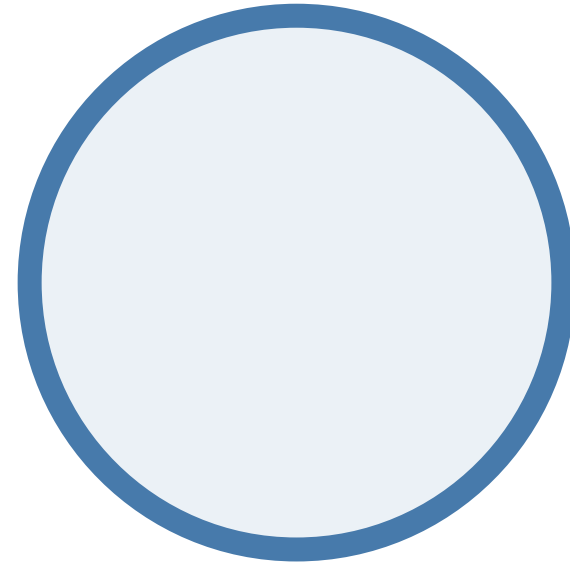
- Type II pneumocyte hyperplasia is a listed morphologic feature.
- Type II cells normally synthesize surfactant and repair injured alveolar lining.
- Thus the affected cell population is also an epithelial repair population.

Schematic — not a histologic specimen

Interstitial fibrosis adds a restrictive lung component



Normal thin septa



Thickened fibrotic septa

Native schematic: Septal thickness is illustrative, not measured.

Alveolar simplification indicates architectural change

- Alveolar simplification is part of the morphologic spectrum.
- It should be interpreted with the accompanying epithelial and interstitial findings.
- The short textbook section does not assign simplification to one gene alone.
- Architectural abnormality is not equivalent to a genotype-specific histologic diagnosis.

Histologic findings are variable, not pathognomonic

Finding	Meaning for interpretation
Pink granular intraalveolar material	Supports an airspace component; not specific
Type II pneumocyte hyperplasia	Shows involvement of the surfactant-producing epithelium
Interstitial fibrosis	Explains a chronic interstitial phenotype
Alveolar simplification	Signals altered alveolar architecture

Protein immunohistochemistry: Intended target matters

Surfactant protein B deficiency

- IHC may demonstrate lack of SP-B.
- A negative stain must be interpreted for the relevant deficiency.

Surfactant protein C deficiency

- IHC may demonstrate lack of SP-C.
- An abnormal stain is not a complete stand-alone molecular characterization.

IHC findings and genetic findings answer different questions

IHC
Protein expression

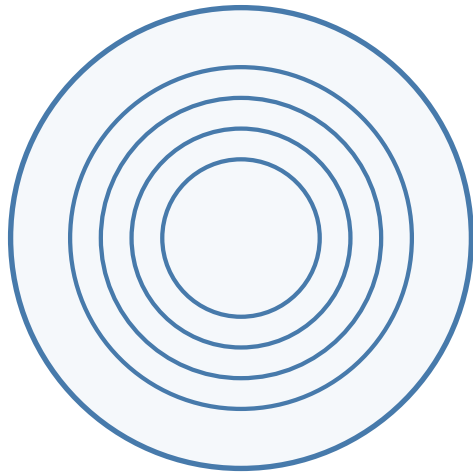
Morphology
Tissue response

Ultrastructure
Organelle
phenotype

Genetics
Gene-level etiology

Integrated interpretation prevents treating a single microscopic feature as a universal genotype assay.

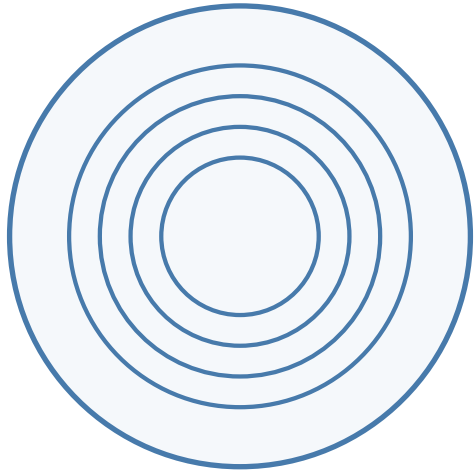
Lamellar bodies are an ultrastructural diagnostic compartment



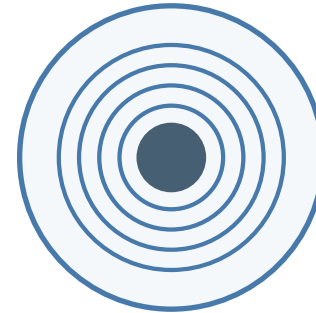
- Lamellar bodies occur within type II pneumocytes.
- All three genetic groups may exhibit ultrastructural abnormalities.
- The source specifically singles out a characteristic ABCA3-associated pattern.

Schematic — not electron microscopy

ABCA3: Small lamellar bodies with dense cores



Conceptual normal lamellation



ABCA3-associated small, dense-core pattern

Schematic only — the original textbook electron micrograph is not reproduced.

Electron microscopy provides a high-value clue

- Small lamellar bodies containing electron-dense cores are characteristic of ABCA3-associated disease.
- This organelle pattern directly links an epithelial transporter to ultrastructure.
- The textbook regards this pattern as diagnostic for ABCA3 mutation.
- No electron micrograph has been reproduced in this lecture.

The ultrastructural phenotype differs from PAP

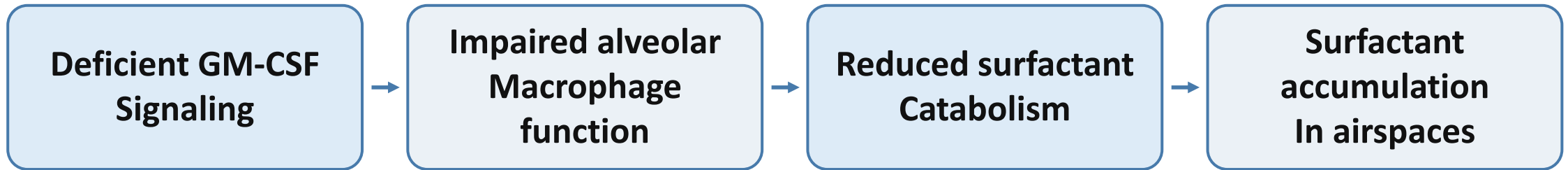
Genetic surfactant dysfunction

- Lamellar-body abnormalities within type II cells
- ABCA3 has a characteristic dense-core pattern
- May also show alveolar and interstitial injury

Pulmonary alveolar proteinosis

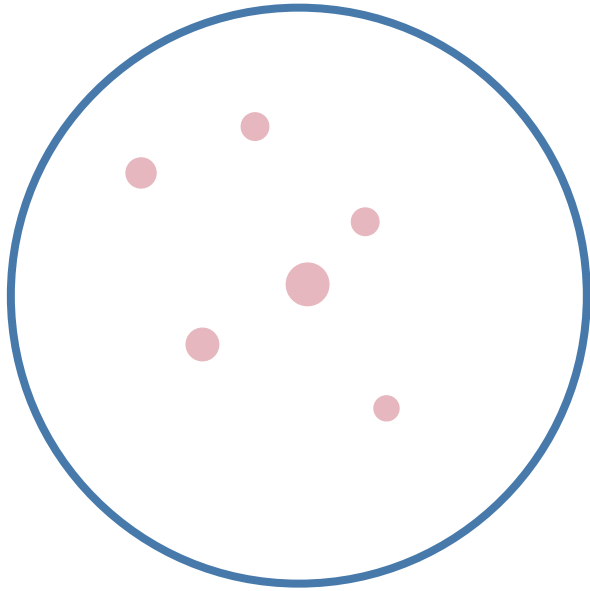
- Lamellar bodies in type II cells are normal
- Macrophage-mediated clearance is defective
- Surfactant-rich material fills airspaces

Pulmonary alveolar proteinosis: Clearance failure



This is a macrophage-centered mechanism, not the same primary lesion as ABCA3/SFTPB/SFTPC dysfunction.

PAP: Alveolar deposits with relatively preserved walls



PAP-like airspace filling

- PAP has abundant surfactant-containing intraalveolar precipitates.
- Minimal inflammation and normal alveolar walls in its illustrated case.
- Type II-cell lamellar bodies are ultrastructurally normal.

Schematic — not a PAP histology micrograph

PAP and inherited surfactant dysfunction: Practical contrast

Feature	PAP	Genetic dysfunction
Primary process	Impaired clearance	Altered trafficking / secretion
Key compartment	Alveolar macrophage	Type II pneumocyte
Lamellar bodies	Typically normal	May be abnormal
Microscopic emphasis	Airspace deposits	Deposits + epithelial/interstitial changes

An inherited condition is not the same as every congenital PAP

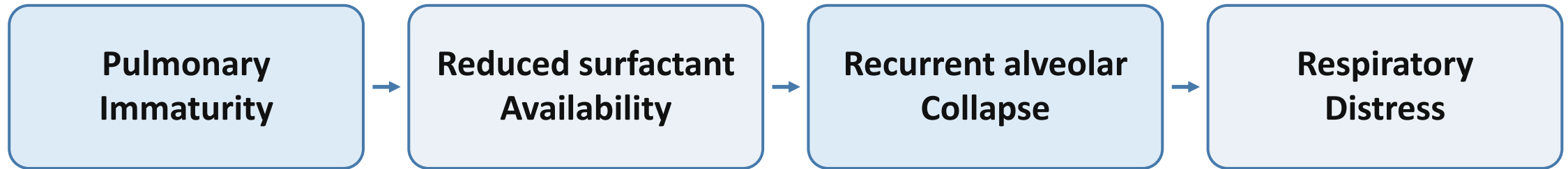
Hereditary PAP

- Defect in GM-CSF or GM-CSF receptor genes
- Very rare neonatal presentation
- Problem is impaired macrophage signaling

Genetic surfactant dysfunction

- ABCA3, SFTPC or SFTPB pathway
- Transport or protein biology is affected
- Abnormal type II-cell lamellar bodies possible

Premature-infant RDS: The mechanism is developmental



This pathway is distinct from an inherited surfactant protein or transporter defect.

RDS and genetic disease share a downstream consequence

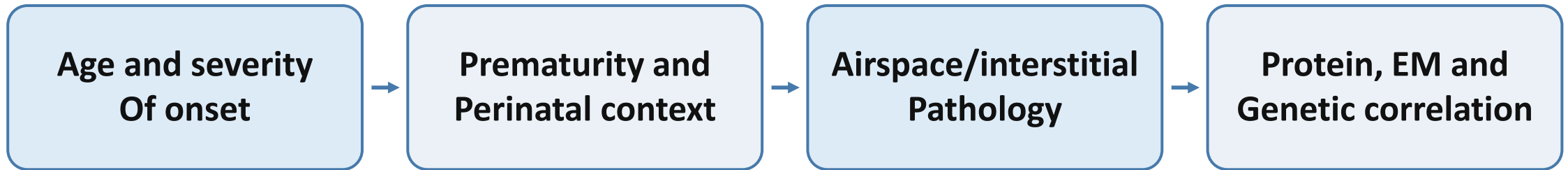
Shared consequences

- Reduced effective surface tension control
- Poor alveolar stability
- Respiratory distress and impaired gas exchange

Different starting lesions

- Immaturity of surfactant synthesis in typical neonatal RDS
- Mutations in surfactant pathway proteins in inherited disease
- Different prognostic patterns and context

Diagnostic synthesis starts with the clinical pattern



Teaching synthesis — not a validated clinical testing algorithm.

Gene-oriented interpretation of clinical clues

Observation

Genetic association suggested by Robbins

Severe disease in first few months

Common ABCA3 presentation

Full-term infant with rapid postnatal decline

Typical severe SFTPB-deficient pattern

Dominant-family pattern with variable course

SFTPC-compatible clinical context

Chronic ILD in older child or adult

Can occur with ABCA3; not gene-specific

Pathology-oriented interpretation of morphologic clues

Observation	Interpretation / limitation
Pink granular alveolar material	Nonspecific; consider PAP among the differential
Type II hyperplasia and fibrosis	Compatible with surfactant-associated epithelial injury
Lack of SP-B or SP-C on IHC	Supports the corresponding protein deficiency in context
Small lamellar bodies with dense cores	Characteristic ABCA3-associated EM finding

Case 1: Severe disease in a full-term newborn

A full-term infant develops progressive respiratory distress shortly after birth.

- Which inherited surfactant disorder has this typical presentation?
- What inheritance pattern would be expected?
- What could surfactant-protein immunostaining show?

Case 1: Interpret the pattern



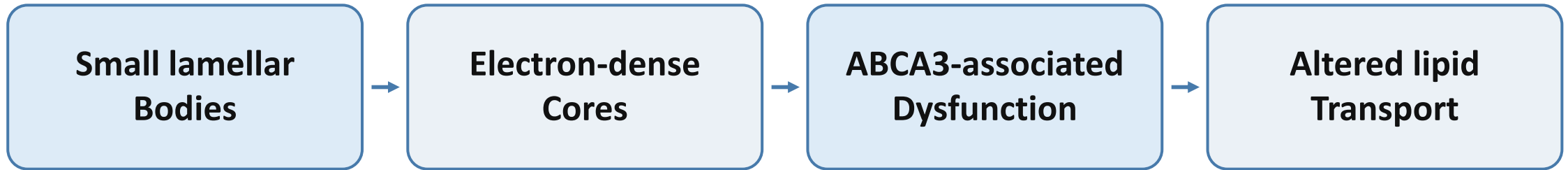
Autosomal recessive inheritance; Absent SP-B may be detected by IHC in the deficiency phenotype.

Case 2: An infant with abnormal lamellar bodies

An infant develops respiratory failure. Electron microscopy reveals small lamellar bodies containing dense cores.

- Which gene is specifically associated with this ultrastructural appearance?
- Which normal protein function does that gene support?

Case 2: Use ultrastructure mechanistically



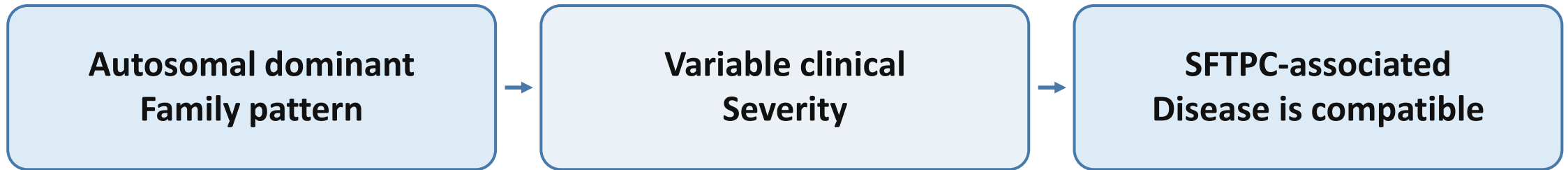
The source designates the dense-core lamellar-body pattern as diagnostic for ABCA3 mutation.

Case 3: Variable familial interstitial disease

Several relatives develop interstitial lung disease of differing severity; The pedigree is compatible with dominant inheritance.

- Which surfactant protein gene belongs in the differential?
- Why must the disease severity remain an open question?

Case 3: Inheritance is useful but not definitive



A compatible pedigree does not replace molecular confirmation or exclude other inherited ILD causes.

Integrated gene–phenotype–morphology map

Disease gene	Presentation emphasized	Pathology clue
ABCA3	Infant respiratory failure; occasional later ILD	Small dense-core lamellar bodies
SFTPC	Autosomal dominant; highly variable	Loss of SP-C may be seen on IHC
SFTPB	Full-term neonate; rapidly progressive	Loss of SP-B may be seen on IHC

Five conclusions to retain

- Genetic surfactant disorders are type II-cell-centered diseases with diverse presentations.
- ABCA3 is the leading gene; The distinctive EM clue is a dense-core lamellar body.
- SFTPC disease is autosomal dominant and clinically heterogeneous.
- Severe SFTPB deficiency classically affects full-term neonates.
- Differentiate impaired production/handling from PAP-related failure of clearance.

Reference and scope of this lecture

- Primary source: Robbins, Cotran & Kumar, Pathologic Basis of Disease, 11th ed. (2026), “Surfactant Dysfunction Disorders.”
- Related pathology context: alveolar anatomy, pulmonary alveolar proteinosis and genetic interstitial fibrosis.
- Physiologic context: surfactant maturation and neonatal respiratory distress syndrome.
- Schematic figures are original, editable teaching graphics; they are not observed specimens.