

α 1-Antitrypsin deficiency

Molecular pathogenesis • hepatic morphology • pulmonary disease

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Learning outcomes

- Explain how the same variant causes distinct liver and lung injury.
- Interpret Pi nomenclature and genotype–phenotype relationships.
- Recognize the characteristic PAS–diastase-resistant hepatocellular globules.
- Connect panacinar emphysema to antiprotease loss and clinical progression.

One gene, two organ mechanisms

SERPINA1 / α 1AT variant

Defective secretion + ER retention

Liver: Toxic protein accumulation

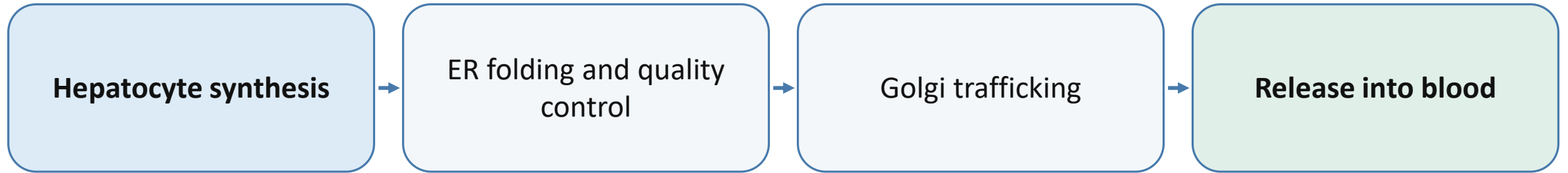
Lung: Antiprotease deficiency

The hepatic and pulmonary lesions arise by different mechanisms.

Core definition

- Inherited disorder of α 1-antitrypsin protein folding and secretion.
- Circulating antiprotease levels are markedly reduced in severe deficiency.
- Hepatic retention of mutant protein and pulmonary antiprotease failure coexist.

Where α 1-antitrypsin is made



Normal α 1AT reaches tissues after hepatocyte production.

Protein identity

- α 1-antitrypsin (α 1AT or AAT) is a plasma glycoprotein.
- The mature protein contains 394 amino acids.
- It is a member of the serine protease inhibitor (serpin) family.

Main physiologic targets

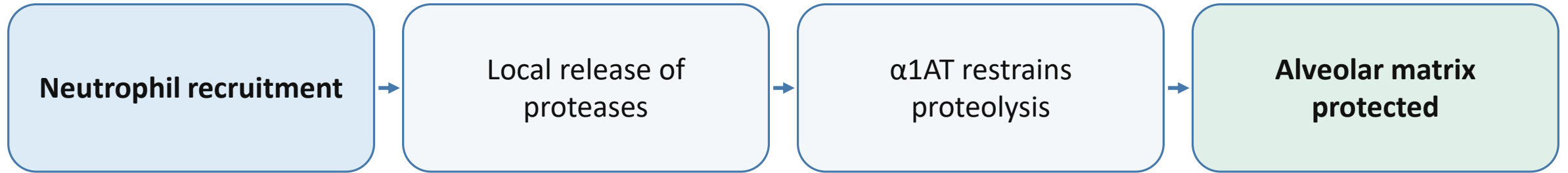
Neutrophil elastase

Cathepsin G

Proteinase 3

These proteases are released by neutrophils at inflammatory sites.

The normal pulmonary balance



Protection depends on an effective protease–antiprotease balance.

Why genetic nomenclature uses “Pi”

- “Pi” abbreviates protease inhibitor.
- Protein variants were originally distinguished by electrophoretic migration.
- Two letters designate the pair of inherited alleles.

Major genotypes at a glance

PiMM: Usual protein

PiMZ: Intermediate level

PiZZ: Severe deficiency

Serum expression shows codominance; Severe clinical disease is usually associated with two deficient alleles.

PiMM: Reference genotype

- PiMM is the most common genotype in the Robbins description.
- It is the usual (wild-type) reference for protein level.
- PiMM in approximately 90% of individuals.

PiMZ: Intermediate plasma concentration

- The M and Z alleles are both expressed.
- A PiMZ carrier produces an intermediate plasma concentration of α 1AT.
- Intermediate level does not imply that every carrier develops clinically apparent disease.

PiZZ: High-risk genotype

- PiZZ homozygotes have very low circulating α 1AT.
- Levels at approximately 10% of normal.
- Severe antiprotease deficiency predisposes to emphysema; Intracellular Z protein predisposes to hepatic injury.

Genotype, protein level, and mechanism

Genotype	Circulating α 1AT	Hepatic Z protein
PiMM	Reference/normal	Absent
PiMZ	Intermediate	One Z allele may contribute retention
PiZZ	~10% of usual level	Marked ER retention

Population context and limits

- PiZZ in approximately 1 of 1,800 live births among people of Northern European descent.
- That estimate must not be generalized to all populations.
- Genotype prevalence is not equivalent to the prevalence of clinical cirrhosis or emphysema.

Loss of function versus toxic gain of function

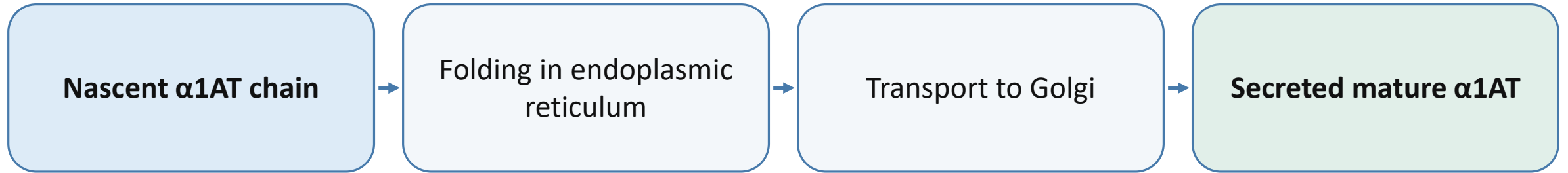
Lung injury

- Too little active circulating α 1AT
- Excess neutrophil protease activity
- Alveolar septal destruction

Liver injury

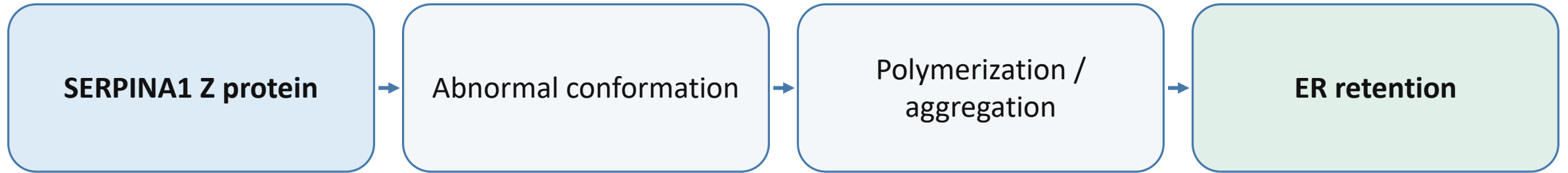
- Mutant Z protein retained in hepatocytes
- ER stress and unfolded protein response
- Cell injury and potential apoptosis

Normal intracellular trafficking



A secretion-competent fold permits exit from the ER.

Z protein: Blocked export

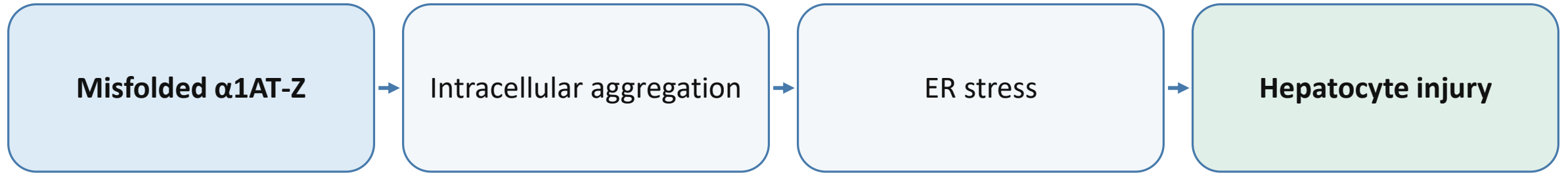


A defect in folding and ER-to-Golgi transport lowers secretion.

Z allele: Correct molecular designation

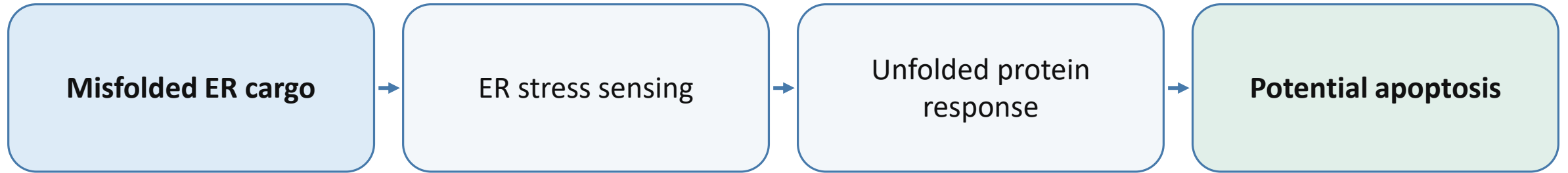
- The canonical Z substitution is Glu342Lys (E342K), using mature-protein numbering.
- The variant favors misfolding and polymer formation.
- Robbins' converted text says "glutamine"; Authoritative molecular references specify glutamic acid.

Protein retention is a hepatocyte insult



This injury requires the retained mutant product, not simply absence from blood.

Unfolded protein response



The response is initially adaptive but prolonged stress can damage cells.

Why the liver mechanism is “toxic gain of function”

- The mutant molecule acquires an injurious propensity to accumulate.
- Intracellular aggregates activate stress responses in producing hepatocytes.
- The liver phenotype is not explained by loss of extracellular elastase inhibition.

Incomplete hepatic penetrance

- PiZZ hepatocytes characteristically retain α 1AT-Z.
- Only a subset of PiZZ individuals develops overt hepatic disease.
- Additional genetic and environmental modifiers, not yet specified in that section.

Shared genotype, divergent organ outcomes

Severe lung phenotype

- Low antiprotease activity
- Protease-driven extracellular injury
- Smoking markedly accelerates disease

Severe hepatic phenotype

- Retention of misfolded protein
- Intracellular stress and tissue remodeling
- Variable penetrance despite globule accumulation

Hepatic disease across the lifespan

- Presentations range from infancy to adult life.
- Severe infantile cases can progress rapidly toward cirrhosis.
- Other individuals present as adults with chronic hepatitis, cirrhosis, or hepatocellular carcinoma.

Characteristic hepatocellular inclusions

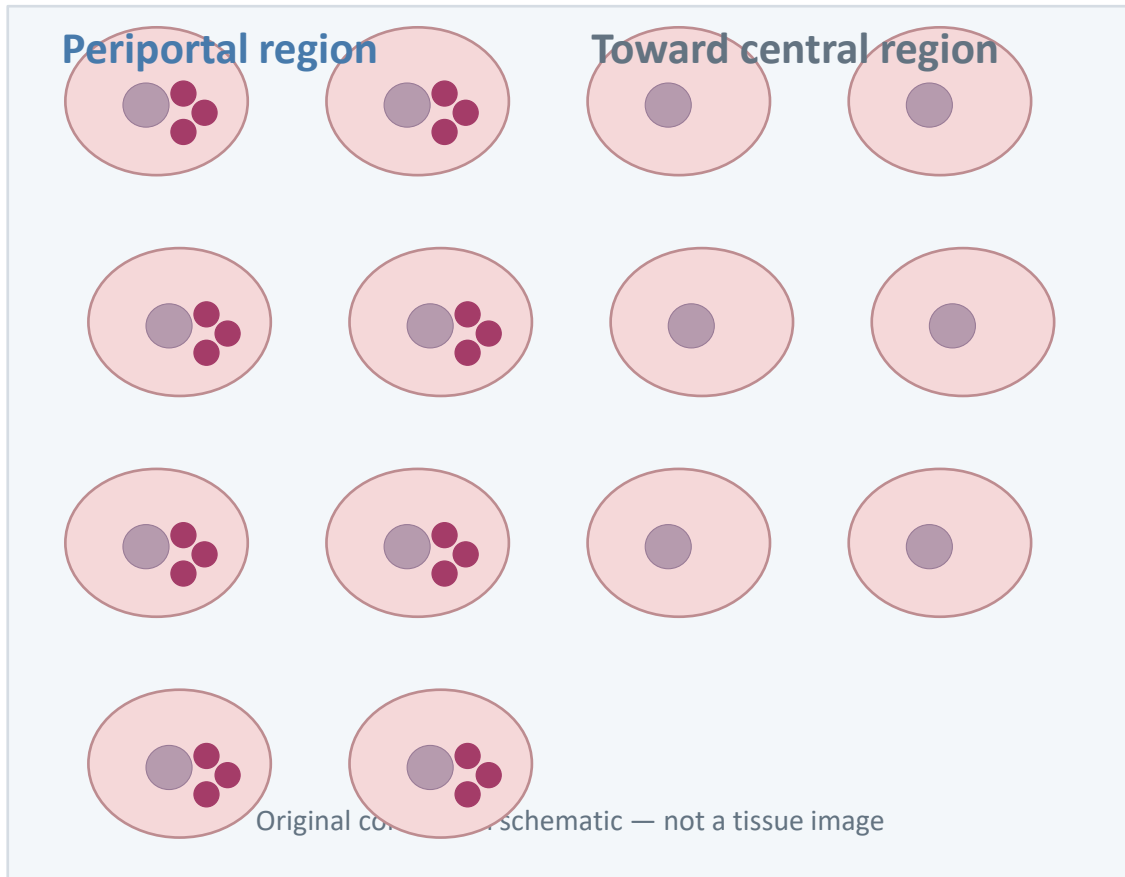


- Round-to-oval cytoplasmic globules
- Most conspicuous on PAS after diastase
- Reflect accumulated mutant α 1AT

Why PAS–diastase highlights globules

- The retained glycoprotein is PAS-positive.
- Diastase removes PAS-reactive glycogen; Characteristic α 1AT inclusions persist.
- The expected histologic signal is magenta cytoplasmic globules.

Periportal predominance in early disease



- Globules initially appear in periportal hepatocytes.
- More advanced disease may involve central hepatocytes.
- Zonal location reflects pattern of retention—not a stand-alone measure of injury.

Globule count is not a severity score

- The proportion of globule-bearing hepatocytes correlates poorly with disease severity.
- The diagnostic inclusion and the magnitude of ongoing injury are different variables.
- A small biopsy cannot reliably stage disease by inclusions alone.

Important neonatal morphology pitfall

- Neonatal hepatitis can precede the development of visible cytoplasmic globules.
- In PiZZ disease, characteristic globules generally emerge at approximately 12 weeks or later.
- Absence of inclusions in early infancy cannot exclude α 1AT deficiency.

What the pathologist should actually identify



- Hepatocellular rather than extracellular globules
- Cytoplasmic, round/ovoid inclusions
- Persistent PAS positivity after diastase

Biopsy findings: Characteristic versus insufficient

Supportive of α 1AT deficiency

- Numerous PAS-D-resistant hepatocyte globules
- Appropriate periportal distribution
- Compatible liver injury pattern

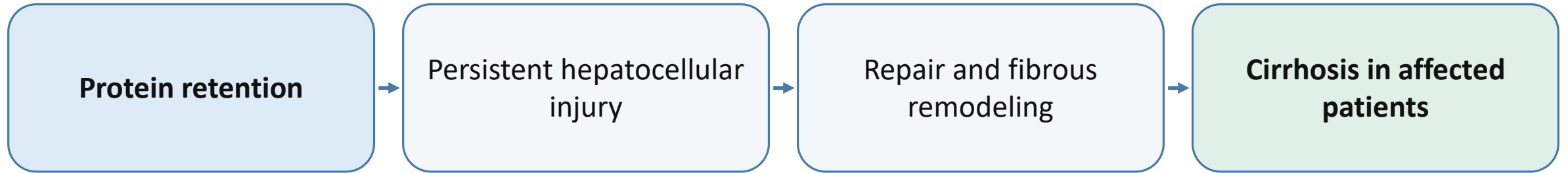
Insufficient as sole evidence

- One isolated nonspecific globule
- Cirrhosis without genotype/biochemical context
- Negative globules in very young infant

Neonatal clinical presentation

- Severe early-onset disease may be recognized as neonatal hepatitis.
- Some severe presentations progress relatively rapidly to cirrhosis.
- The absence of mature PAS-D inclusions early in life is a critical biopsy limitation.

How chronic hepatic injury evolves



Cirrhosis develops in a susceptible subset rather than every PiZZ individual.

Adult hepatic manifestations

- Chronic hepatitis may be the presenting pattern.
- Cirrhosis can follow longstanding hepatic injury.
- Hepatocellular carcinoma is a recognized complication, with or without established cirrhosis.

Hepatocellular carcinoma risk

- Hepatocellular carcinoma in 2%–3% of adults with PiZZ.
- The tumor usually, but not invariably, occurs in a cirrhotic liver.
- This figure is source-specific; It is not an individualized or lifetime prediction.

Hepatic phenotypic spectrum

No overt disease

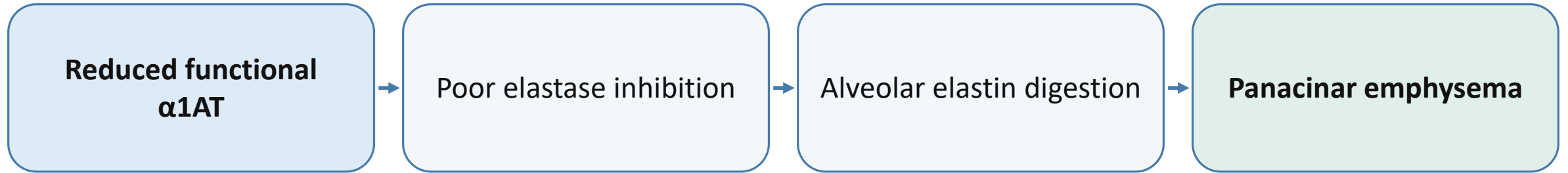
Infantile hepatitis

**Chronic injury /
cirrhosis**

**Hepatocellular
carcinoma**

Clinical trajectories differ despite the same PiZZ genotype.

Why low α 1AT injures the lung



Pulmonary disease is predominantly a loss-of-function phenotype.

Neutrophils as a protease source

- Inflammation recruits neutrophils into lung tissue.
- Activated cells release elastase and related proteases.
- Insufficient inhibitor activity permits ongoing extracellular proteolysis.

Protease–antiprotease balance

Protected alveolus

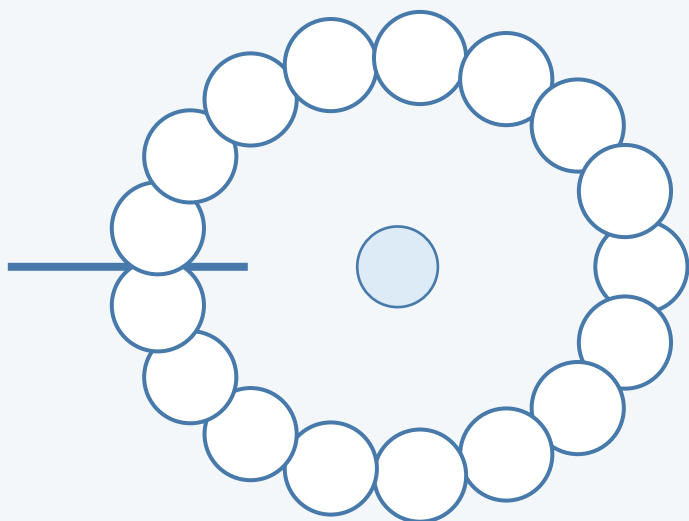
- Physiologic inflammatory protease release
- α 1AT limits elastolytic injury
- Alveolar septa and recoil preserved

Deficient alveolus

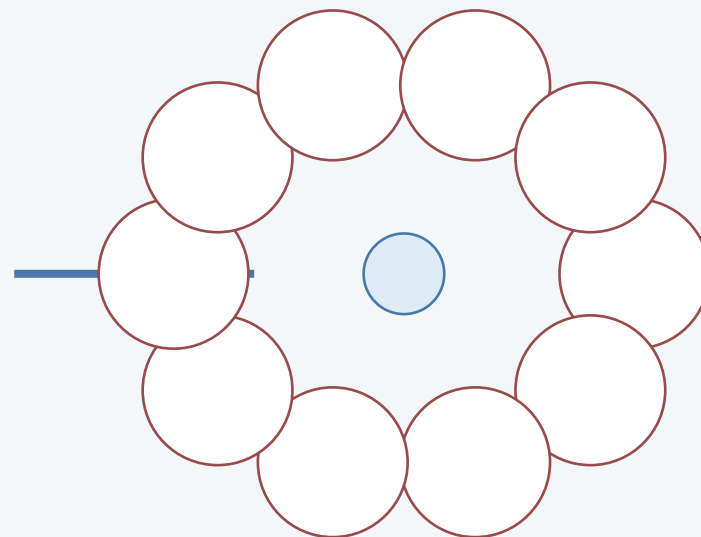
- Same proteases act with less restraint
- Elastin and alveolar walls are damaged
- Recoil and gas-exchange surface are lost

Normal acinus and panacinar enlargement

Normal acinus



Panacinar enlargement



Native schematic — not a histologic specimen.

The panacinar emphysema pattern

- The acinus is diffusely enlarged, from respiratory bronchiole through distal alveoli.
- α 1AT deficiency is a classic cause of this morphologic pattern.
- Alveolar wall destruction decreases elastic recoil and available capillary bed.

Panacinar versus centriacinar emphysema

Panacinar

- Uniform involvement of acinus
- Often lower zones and lung bases
- Strong association with α 1AT deficiency

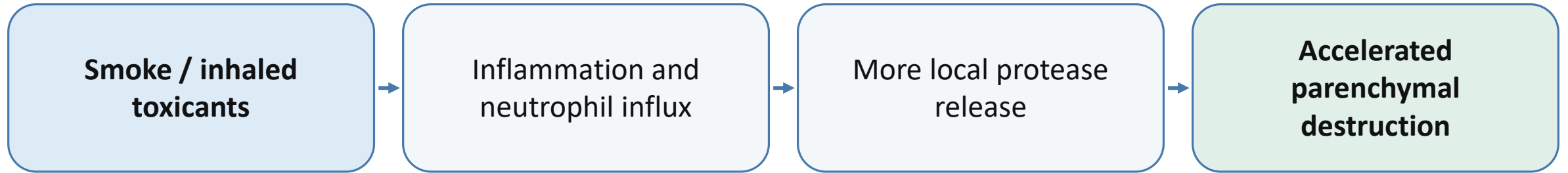
Centriacinar

- Central/proximal acinar involvement first
- Classically upper-lobe predominant
- Strong association with smoking

Lung distribution is a pattern, not a genetic test

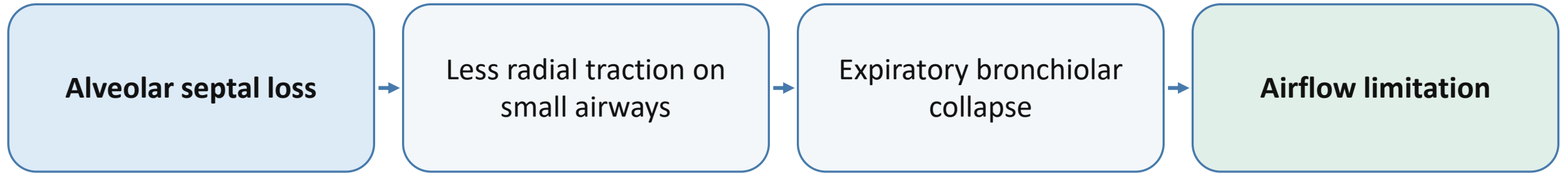
- α 1AT-related panacinar disease is often most severe basally.
- Basal predominance differs from the usual apical tendency of smoking-related centriacinar disease.
- Morphology raises suspicion but is not sufficient to establish genotype.

Smoking magnifies proteolytic damage



Earlier and more severe emphysema in PiZZ individuals who smoke.

Why loss of recoil obstructs airflow

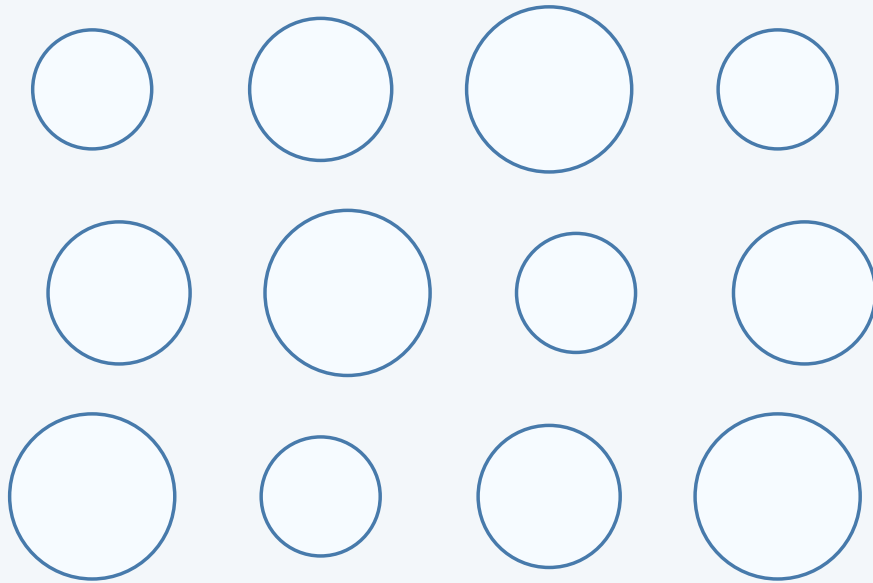


Obstruction can be functional, without a lumen-filling lesion.

Consequences of alveolar destruction

- Enlarged distal airspaces provide less efficient gas-exchange surface.
- Loss of elastic tissue impairs expiratory driving pressure.
- Capillary bed reduction and small-airway collapse contribute to clinical dysfunction.

Lung microscopic morphology: Principles



Enlarged airspaces with reduced septal support

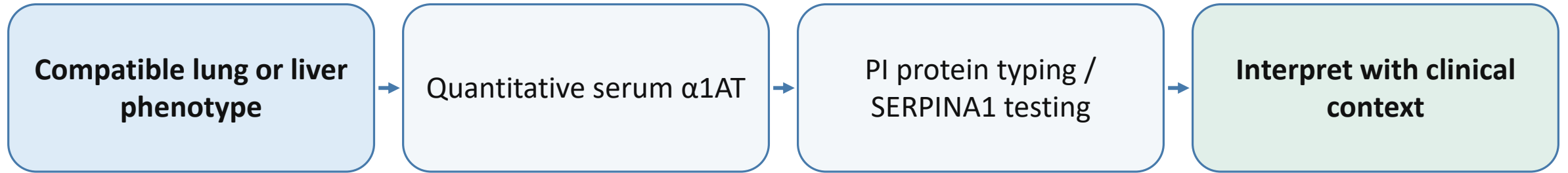
Original conceptual schematic — not a tissue image

- Abnormally enlarged alveolar airspaces
- Thinning and loss of alveolar septa
- Reduced attachments to small airways

Clinical–pathologic interpretation of emphysema

- Panacinar morphology in a young or minimally exposed patient warrants suspicion for severe α 1AT deficiency.
- Smoking history remains an important modifier of risk and presentation.
- Lung morphology and serum genotype address complementary questions.

Diagnostic pathway: Establish the defect



Supplemental clinical diagnostic framework from GeneReviews.

What serum α 1AT measurement tells us

- A low concentration supports a quantitative antiprotease defect.
- It does not by itself resolve every genotype or functional variant.
- Molecular and/or protein phenotyping helps define the cause.

Why genotype or phenotype confirmation matters

- Protein electrophoretic phenotypes and SERPINA1 alleles are related but distinct test outputs.
- PiZZ, PiMZ and other allelic combinations may have different risk profiles.
- Targeted testing may not detect every rare or null allele.

Biopsy and genotype answer different questions

Biopsy

- Shows hepatocellular storage and tissue damage
- Reveals PAS-D globules where present
- May show hepatitis/fibrotic remodeling

Protein / genetic testing

- Demonstrates deficient protein concentration
- Defines electrophoretic phenotype
- Identifies pathogenic SERPINA1 variants

Implications for relatives

- The inherited alleles may be present in family members without clinically evident disease.
- Risk assessment is improved by genotype-aware family evaluation.
- A normal clinical examination is not proof of a usual genotype.

Therapeutic target follows the pathogenesis

Pulmonary component

- Protect against further exposure-driven injury
- Address obstructive lung consequences
- α 1AT augmentation is a pulmonary option in selected patients

Hepatic component

- Monitor for clinically important liver injury
- Advanced liver failure may require transplantation
- Augmentation does not remove hepatic mutant deposits

Liver transplantation: Precise interpretation

- Replacing the diseased liver addresses the hepatic source of retained Z protein.
- With an AAT-replete donor liver, serum α 1AT is restored.
- Pre-existing emphysematous architecture is not reversed by transplantation.

Reconciling the transplantation statements

- Robbins says liver transplantation is curative for hepatic disease but does not alter pulmonary disease.
- Current transplant literature distinguishes restored inhibitor production from persistent established lung destruction.
- Avoid promising that restoration of serum α 1AT repairs existing emphysema.

Case 1 · neonatal liver disease

- An infant with hepatitis undergoes liver biopsy before 12 weeks of age.
- No characteristic PAS-D-resistant globules are identified.
- Question: Does negative globule staining exclude PiZZ-associated disease?

Discussion prompt · interpret the mechanism and limitations

Case 1 · interpretation

- No: Clinically important disease can precede visible inclusion formation.
- The biopsy result must be interpreted in the age-specific morphologic context.
- Protein concentration and phenotype/genotype evaluation can test the hypothesis.

Case 2 · emphysema pattern

- An adult develops airflow obstruction with diffuse panacinar emphysema, predominantly at the lung bases.
- There is a history of cigarette exposure.
- Question: Which inherited defect should enter the differential?

Discussion prompt · interpret the mechanism and limitations

Case 2 · interpretation

- Consider severe α 1AT deficiency as an explanation of the panacinar pattern.
- Smoking is a potent amplifier rather than a reason to disregard genetic risk.
- A protein level and PI/SERPINA1 assessment can establish the molecular basis.

Case 3 · PAS–diastase finding

- A biopsy contains periportal hepatocytes with round magenta cytoplasmic globules persisting after diastase digestion.
- Question: Which intracellular process explains the finding?

Discussion prompt · interpret the mechanism and limitations

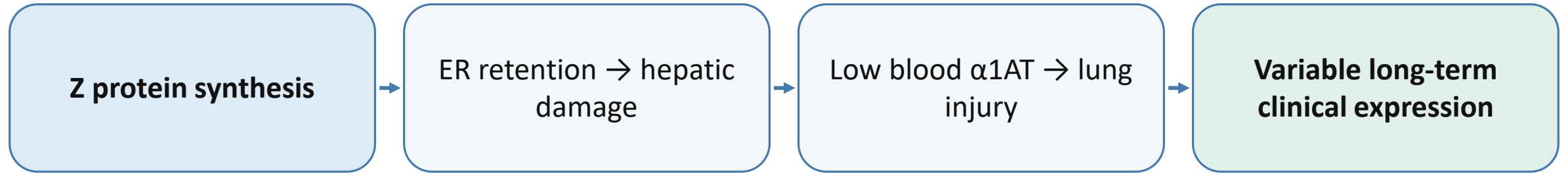
Case 3 · interpretation

- Misfolded mutant α 1AT is retained and aggregates in hepatocyte ER.
- The inclusions indicate abnormal protein handling rather than glycogen accumulation.
- Storage is diagnostically useful but does not independently quantify disease severity.

Distinguishing inherited liver diseases

Disease	Principal defect	Hallmark mechanism
α 1AT deficiency	SERPINA1-related misfolding	ER-retained protein
Wilson disease	ATP7B transport dysfunction	Hepatic copper accumulation
Hemochromatosis	Iron-regulatory defect (often HFE)	Excess iron uptake / deposition

Unified disease model



Liver and lung effects must be evaluated separately.

Key morphologic discriminators

- Hepatic: PAS-positive, diastase-resistant cytoplasmic globules in hepatocytes.
- Pulmonary: Panacinar emphysema, often with basal predominance.
- Neither inclusion count nor lung topography alone predicts individual genotype or outcome.

Four high-yield conclusions

- One SERPINA1 variant can cause loss of antiprotease function and toxic intracellular protein retention.
- PiZZ usually produces marked deficiency, but overt hepatic disease has incomplete penetrance.
- PAS–diastase-positive hepatocellular inclusions are characteristic, yet may be absent early in infants.
- Pulmonary destruction and established hepatic injury require distinct clinical assessment.

References and source distinctions

- Primary: Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026), Chapter 18, pp. 774–775; pulmonary context Chapter 15, pp. 618–620.
- Supplemental molecular correction: MedlinePlus Genetics, SERPINA1; GeneReviews® Alpha-1 Antitrypsin Deficiency (updated 2023).
- Supplemental clinical/transplant interpretation: Zamora et al., Ther Adv Chronic Dis (2021), PMCID: PMC8367211.
- All organ and cell illustrations in this deck are original editable schematics—not histologic or radiologic specimens.