

Pathogenesis and Classification of Amyloidosis

Protein misfolding • fibril formation • biochemical and clinical categories

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Learning objectives

Trace normal protein quality control to insoluble extracellular fibrils.

Distinguish precursor overproduction from genetically variant proteins.

Classify deposits by biochemical precursor and tissue distribution.

Apply the classification to AL, AA, ATTR and selected localized forms.

Interpretation

Classification begins with the fibril protein—not solely the organ or associated disease.

Amyloidosis: The unifying lesion

Proteins prone to aggregation assemble into extracellular fibrillar deposits.

Their persistence progressively impairs tissue architecture and function.

Amyloidosis denotes a family of disorders, not a single protein disease.

Interpretation

Common histologic appearance can conceal markedly different precursors.

Why one morphology has many etiologies

More than 40 proteins can form amyloid, according to the textbook.

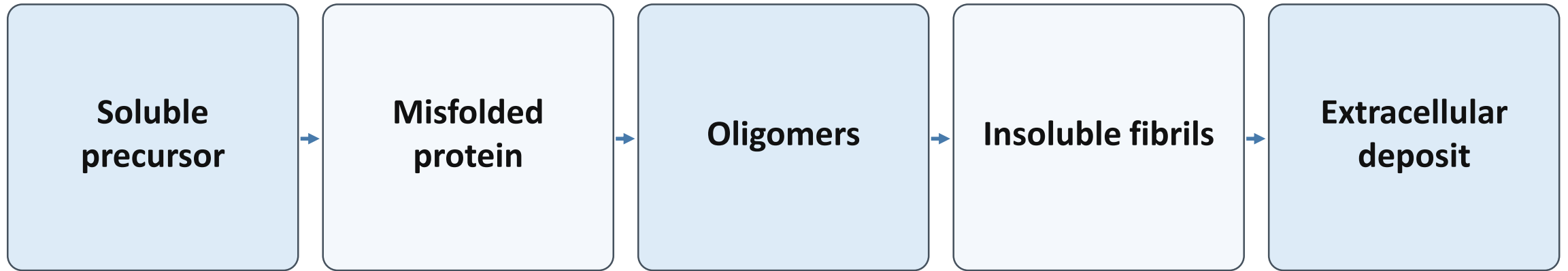
Different precursor proteins reach a shared fibrillar conformation.

Disease classification therefore depends on chemical identity and context.

Interpretation

Morphologic similarity does not establish an AL, AA or ATTR subtype.

From precursor to tissue damage



The key transition is formation of aggregation-prone conformations.

Accumulation, persistence and tissue location determine the consequences.

Amyloid is extracellular

Aggregates coalesce into fibrils deposited between cells and in matrices.

Deposits may accumulate next to basement membranes and blood vessels.

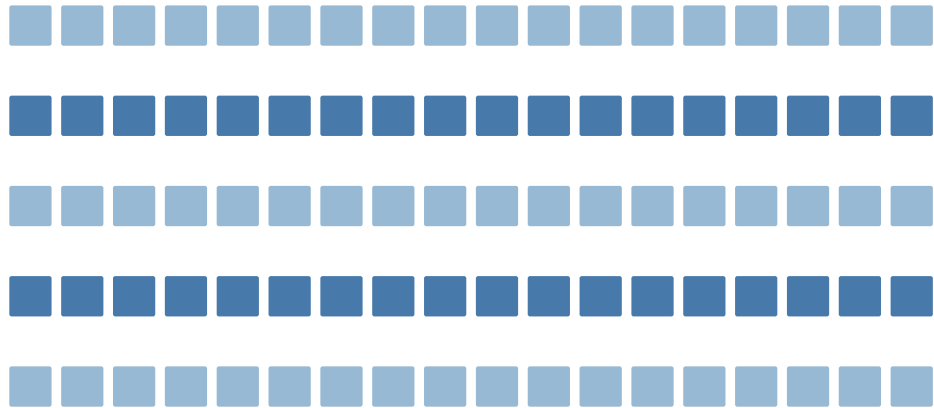
Expanding material compresses adjacent parenchymal structures.

Interpretation

The deposited material lies outside cells even when the precursor originates intracellularly.

Common fibril architecture

Schematic — fibril arrangement



Nonbranching parallel organization

Mechanistic interpretation

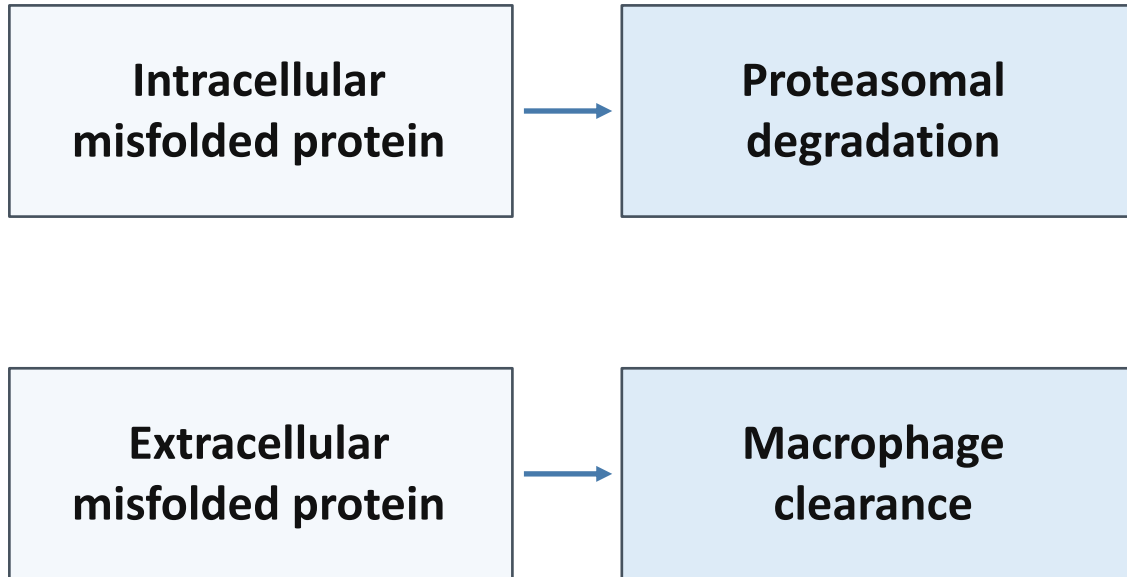
Electron microscopy: Nonbranching fibrils approximately 8–10 nm in diameter.

A cross- β -pleated organization underlies their common structural behavior.

The shared fibrillar geometry helps explain the Congo red reaction.

Normal protein surveillance

Schematic — two parallel disposal routes



Mechanistic interpretation

Intracellular misfolded proteins are typically removed by proteasomes.

Extracellular misfolded proteins can be cleared by macrophages.

These are parallel quality-control systems, not sequential steps.

Two major routes to amyloidogenesis

Route 1: Excess / persistence

A normal protein is intrinsically capable of misfolding.

Overproduction or reduced degradation increases its available pool.

Examples: Light chains, SAA and wild-type TTR.

Route 2: Altered sequence

A variant protein is structurally more prone to abnormal folding.

Aggregation may occur despite production at ordinary levels.

Example: Pathogenic variant transthyretin.

Both routes converge on insoluble fibrils and tissue deposits.

Amyloidogenesis is a balance problem

Precursor synthesis continuously supplies potentially amyloidogenic protein.

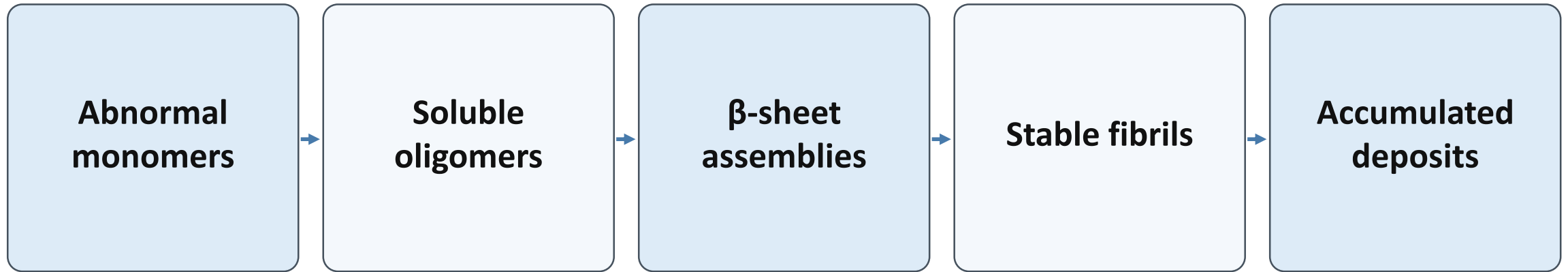
Proteolysis and cellular clearance constrain its effective concentration.

More substrate, less clearance or greater misfolding propensity shifts the balance.

Interpretation

Failure of protein-quality control as a key permissive event.

Molecular assembly proceeds in stages

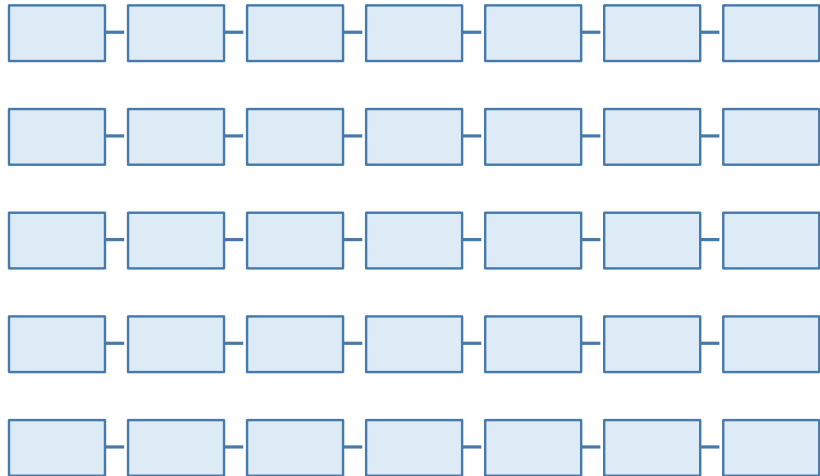


Oligomer formation precedes large insoluble fibrillar aggregates.

Stage labels describe a conceptual sequence, not a kinetic timescale.

Why β -structure matters

Schematic — repeated β -sheet packing



Stacking and side-chain interactions stabilize an ordered fibril.

Mechanistic interpretation

Amyloidogenic monomers adopt a β -sheet-rich structure.

Stacked protofilaments assemble into nonbranching fibrils.

This arrangement—not precursor identity—underlies shared staining properties.

Deposits contain more than fibril protein

Amyloid associates with proteoglycans and glycosaminoglycans.

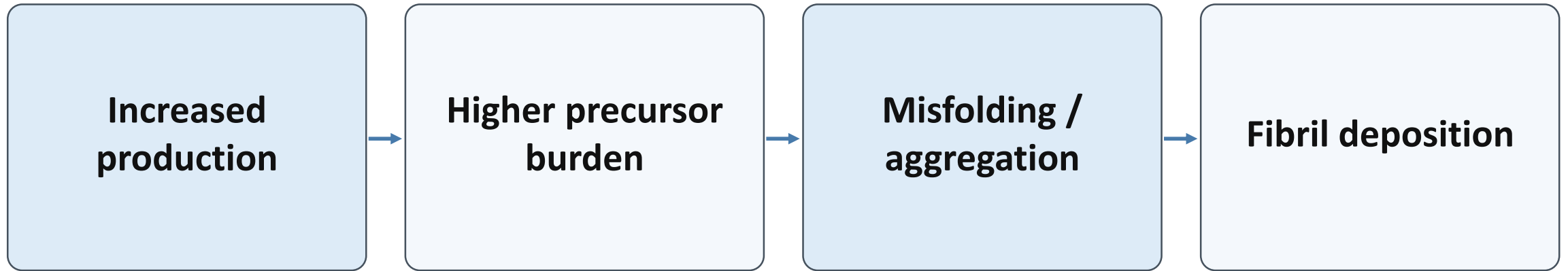
Heparan sulfate, dermatan sulfate and serum amyloid P-component occur in deposits.

These associated molecules coexist with the dominant fibrillar precursor.

Interpretation

Fibrillar protein as the great majority of the deposit.

Excess precursor: General mechanism



Normal sequences can become amyloidogenic when precursor load is excessive.

Reduced breakdown can act as an additional contributor.

Immunoglobulin light chain: AL pathway



The fibril protein is immunoglobulin light chain or a fragment.

The plasma-cell clone is the source, not the identity of the deposited fibril.

AL precursor identity

AL denotes amyloid light chain, derived from monoclonal immunoglobulin light chains.

Deposits contain complete light chains, amino-terminal fragments, or both.

The source notes λ chains predominate, although κ chains also form amyloid.

Interpretation

The prefix AL specifies the fibril protein; It does not mean every monoclonal gammopathy causes amyloid.

Why only some free light chains aggregate

Plasma-cell proliferations can release large quantities of free light chains.

Most patients with circulating light chains do not develop amyloidosis.

Sequence-dependent physicochemical properties influence amyloidogenicity.

Interpretation

Abundance alone is insufficient:
The particular light-chain sequence matters.

AL may occur without overt myeloma

An underlying monoclonal plasma-cell proliferation remains the mechanism.

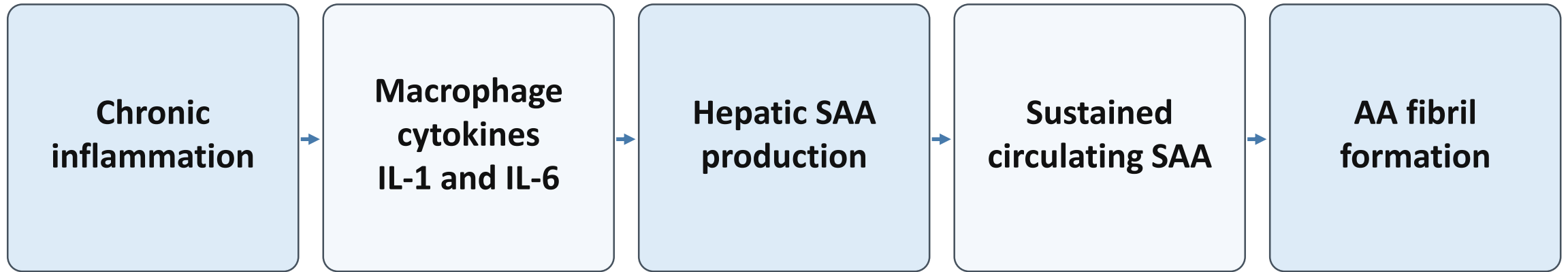
Classical myeloma features need not be evident when amyloid causes disease.

Monoclonal immunoglobulin and/or free light chains are usually detectable.

Interpretation

“Primary” is a historical clinicopathologic label; AL is the biochemical name.

Inflammation supplies the AA precursor



Serum amyloid A (SAA) is an acute-phase precursor.

Long-standing inflammatory activity sustains its hepatic synthesis.

SAA is not itself deposited unchanged

Serum amyloid A circulates as a plasma acute-phase protein.

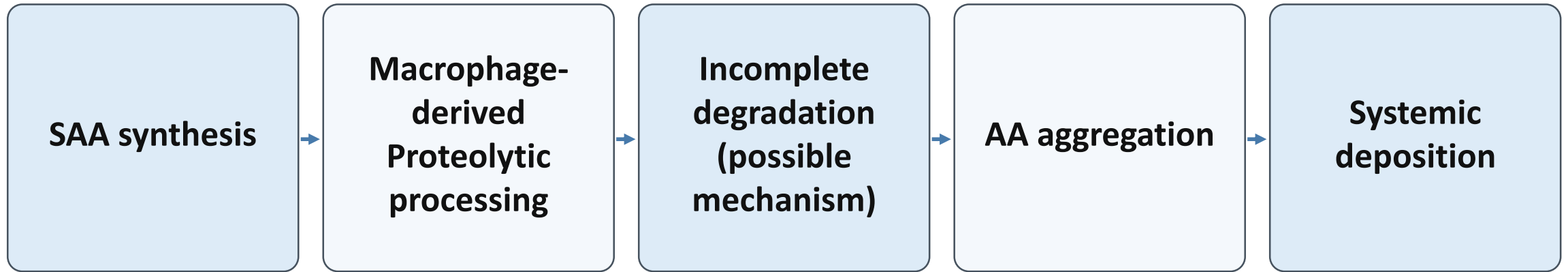
Proteolysis of the SAA precursor yields amyloid A (AA) fibril protein.

Persistent excess SAA increases substrate available for amyloidogenesis.

Interpretation

Precursor SAA and deposited AA are chemically related but not interchangeable labels.

AA formation involves impaired processing



Normal degradation yields soluble products.

The book discusses defective breakdown or resistant SAA structure as possible explanations.

AA mechanism: Established vs proposed

Established: Inflammation increases SAA production through acute-phase signaling.

Established: Fibrils contain AA, generated from the SAA precursor.

Proposed: Incomplete macrophage degradation and/or structural resistance aid deposition.

Interpretation

Do not present proposed processing abnormalities as proven in every patient.

AL and AA: Different upstream causes

AL: Monoclonal protein

Plasma-cell clone supplies a particular light-chain sequence.

Free light chain or fragments form the deposited fibril.

Associated with monoclonal plasma-cell disorders.

AA: Inflammatory response

Inflammatory cytokines increase hepatic SAA synthesis.

SAA-derived AA forms the deposited fibril.

Associated with chronic inflammatory diseases.

Both cause extracellular amyloid despite distinct source cells.

ATTR begins with transthyretin

Transthyretin (TTR) is a circulating transport protein.

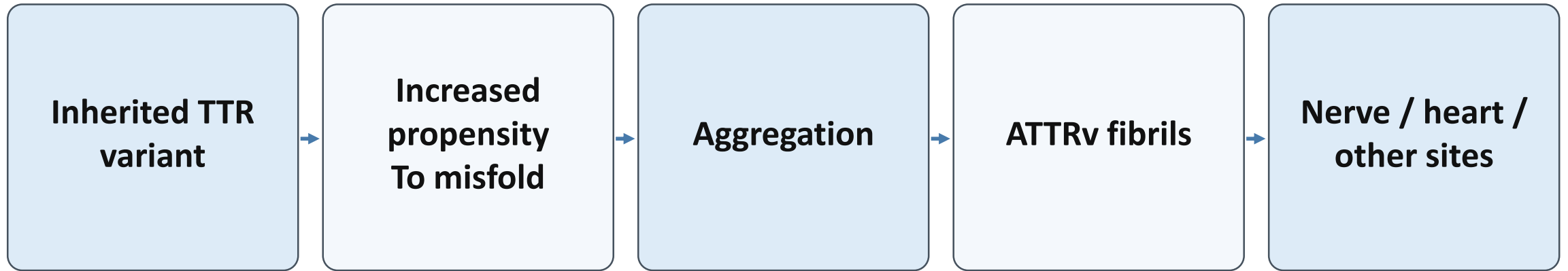
Its normal functions include binding and transport related to thyroxine and retinol.

Both wild-type and variant TTR can form amyloid under different conditions.

Interpretation

ATTR specifies transthyretin-derived fibrils, not an exclusively cardiac disease.

Variant TTR: Sequence-mediated pathway



Specific variant polypeptides can favor distinct organ patterns.

The source describes ATTRv as autosomal dominant.

ATTRv illustrates a normal-quantity problem

The pathogenic property may reside in the amino-acid sequence.

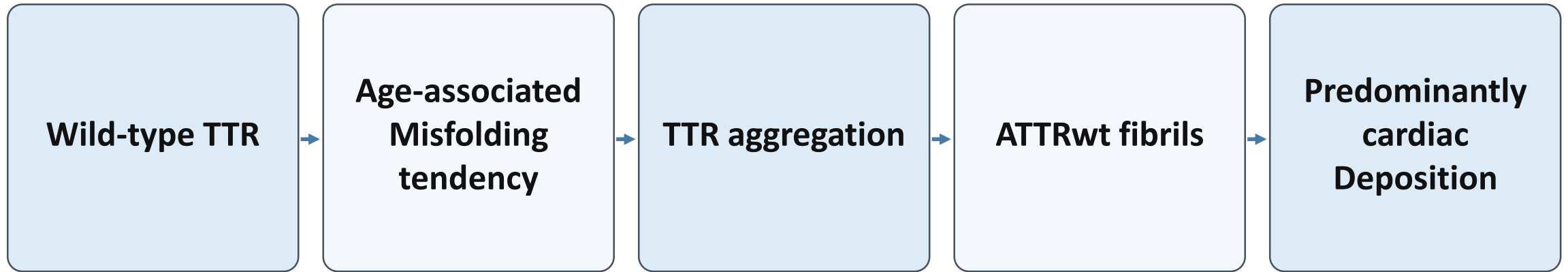
A variant precursor can misfold without exceptional overproduction.

Extracellular fibril assembly produces clinically important deposits.

Interpretation

Variant protein production contrasts mechanistically with sheer precursor excess.

Wild-type TTR: Aggregation with aging



No inherited sequence variant is required for ATTRwt.

Older adults, commonly men, and cardiac involvement.

ATTRwt versus ATTRv

ATTRwt

Protein sequence is wild type.

Typically age-associated; Heart is a major target.

Can also involve connective tissues such as ligaments.

ATTRv

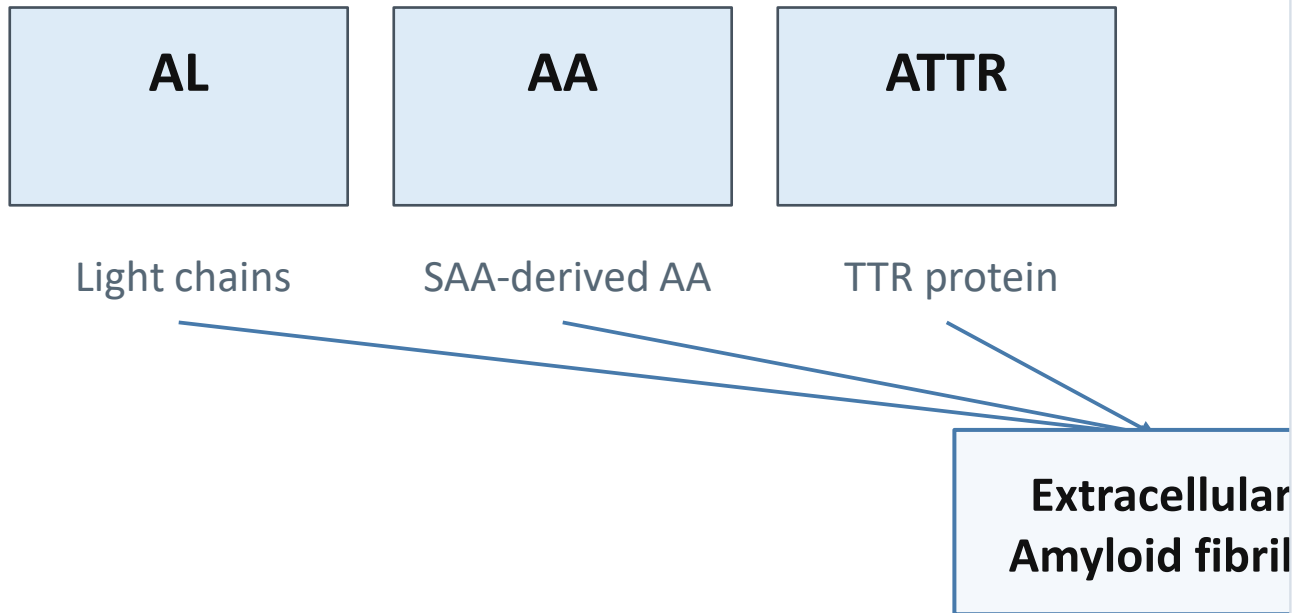
Protein has an inherited amyloidogenic variant.

Autosomal dominant inheritance is described.

Heart, peripheral and autonomic nerves may be affected.

Both are transthyretin amyloidosis; Their etiologic labels are not interchangeable.

Convergent pathogenesis of AL, AA and ATTR



Mechanistic interpretation

AL: Monoclonal light-chain supply and sequence-dependent aggregation.

AA: Cytokine-driven SAA production plus altered processing.

ATTR: Variant or wild-type transthyretin becomes aggregation-prone.

The deposit and the precursor are not synonyms

The circulating or cellular precursor supplies the substrate for fibrils.

Proteolysis may change the deposited protein, as in AA or AL fragments.

Biochemical typing asks which protein constitutes the amyloid fibril.

Interpretation

For classification, name the deposited fibril protein and identify its precursor.

Location: At the source or distant

Localized amyloidosis

Amyloid forms at or near the site of precursor production.

Deposits may remain confined to one organ or tissue.

Some nodular forms are produced by local plasma cells.

Systemic amyloidosis

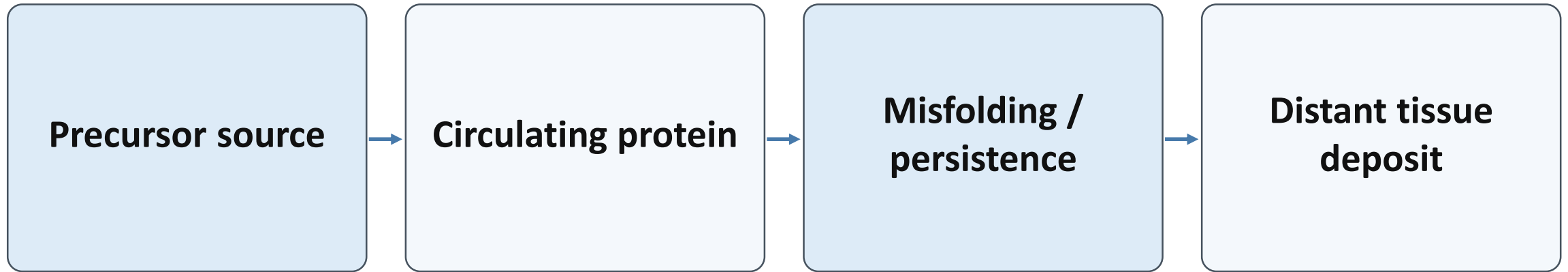
Precursor may circulate from a distant production site.

Deposits accumulate in multiple organs or tissues.

AL, AA and many ATTR forms are central systemic examples.

Distribution is a separate axis from fibril biochemical composition.

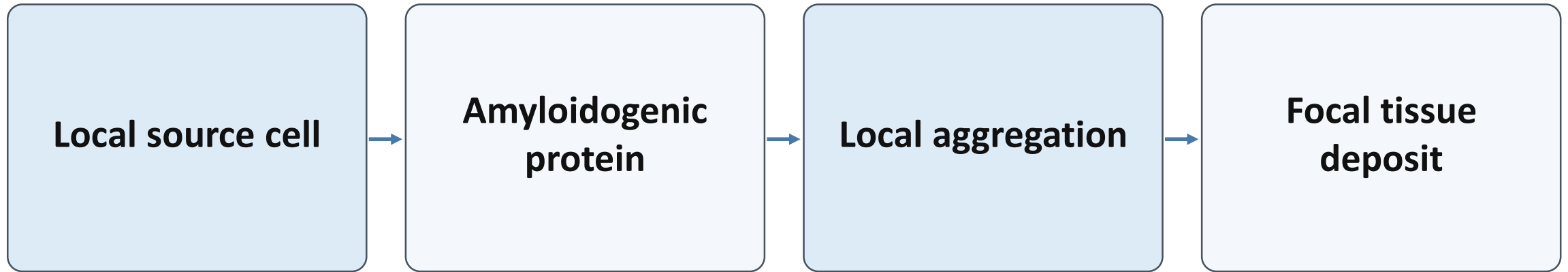
Systemic deposition: Source-to-target separation



Systemic disease is defined by its distribution, not by a unique microscopic morphology.

The exact sites affected vary between patients and subtypes.

Localized deposition: Source and lesion overlap



A single organ can contain amyloid without generalized deposition.

Localized nodules can develop in lung, larynx, skin and other sites.

Classification has independent axes

Protein	AL / AA / ATTR / other
Extent	Localized / systemic
Context	Clonal / inflammatory / inherited / age-related

Mechanistic interpretation

Fibril protein: AL, AA, ATTR and less common types.

Clinical distribution: Systemic or localized.

Etiologic context: Clonal, inflammatory, inherited, age-associated or local.

Biochemical typing is central

Three common forms are designated by the chemical nature of the deposits.

The associated condition provides context but does not replace fibril typing.

The same organ can be affected by different amyloid proteins.

Interpretation

Avoid a classification scheme based only on “primary” and “secondary.”

Three major amyloid families

Fibril type	Immediate precursor	Characteristic context
AL	Ig light chains	Monoclonal plasma-cell proliferation
AA	Serum amyloid A	Sustained inflammation
ATTR	Transthyretin	Wild-type aging or inherited variant

Each row has a distinct precursor; All form extracellular amyloid.

AL is a systemic biochemical category

Usually generalized deposition derived from one amyloidogenic light-chain species.

It is associated with a monoclonal plasma-cell proliferation.

The absence of overt multiple myeloma does not exclude AL amyloidosis.

Interpretation

Etiology: Clone
→ amyloidogenic
light chain →
fibrillar deposits.

AA is the inflammation-linked category

AA is derived from hepatic serum amyloid A rather than an immunoglobulin.

Examples include rheumatoid arthritis and inflammatory bowel disease.

Its deposits are generally systemic classification.

Interpretation

Etiology:
Sustained
inflammatory
signaling → SAA
supply → AA
deposits.

ATTR contains two mechanistically distinct forms

ATTRwt uses the ordinary transthyretin sequence and is age-associated.

ATTRv uses variant transthyretin and may be familial.

Organ predilection can differ even though both contain TTR fibrils.

Interpretation

Genetic status subdivides ATTR; It does not create a different fibril-protein family.

Systemic examples classification

Category	Associated setting	Fibril
AL	Monoclonal plasma-cell disorders	AL
ATTRwt	Aging; heart often affected	ATTRwt
AA	Chronic inflammatory conditions	AA

Table is a teaching abstraction of the textbook Table 6.17.

An involved organ does not identify a subtype

Heart, kidney and other tissues may be affected in multiple amyloid categories.

The textbook cautions against rigid organ-distribution patterns.

Tissue morphology establishes amyloid; Biochemical analysis establishes type.

Interpretation

A cardiac or renal deposit should not automatically be assumed to be AL or ATTR.

Hereditary does not mean one fibril protein

Inherited susceptibility may reflect a variant deposited protein.

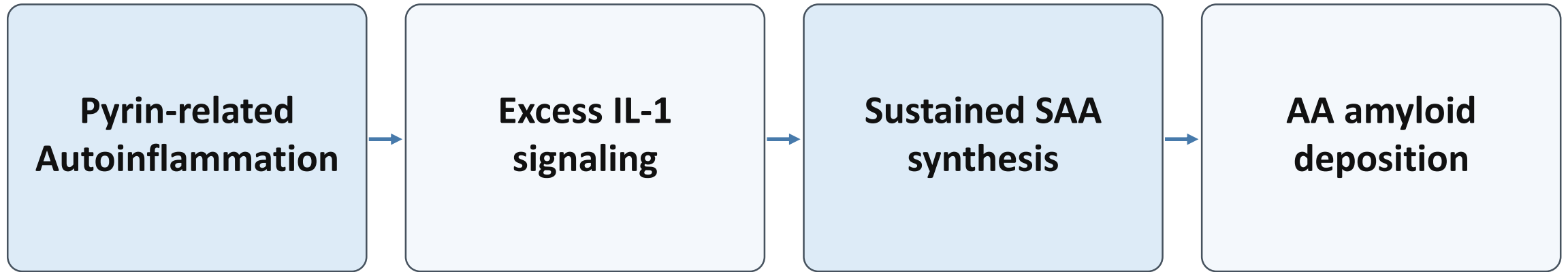
Alternatively, inherited inflammation can increase a normal precursor.

The category “hereditary” therefore overlaps with multiple biochemical classes.

Interpretation

ATTRv has variant
TTR fibrils;
Familial
Mediterranean
fever has AA
fibrils.

Familial Mediterranean fever: Indirect amyloid pathway



The familial disorder is associated with an autoinflammatory syndrome.

The deposited amyloid is AA—not mutant pyrin protein.

Two hereditary mechanisms

Variant fibril protein

ATTRv: Inherited TTR variant is the amyloidogenic substrate.

The molecular change affects precursor fold stability.

Fibril identity follows the variant protein.

Inherited inflammatory driver

Familial Mediterranean fever: Altered inflammatory regulation.

Cytokines raise SAA concentration.

Fibril identity remains AA.

Inherited cause and deposited protein are different classification questions.

Hemodialysis-associated amyloid



β_2 -microglobulin is a normal component of MHC class I and plasma protein.

The burden decreased with newer dialysis filters.

β_2 -microglobulin is a different precursor

The amyloid protein derives from β_2 -microglobulin rather than AL, AA or TTR.

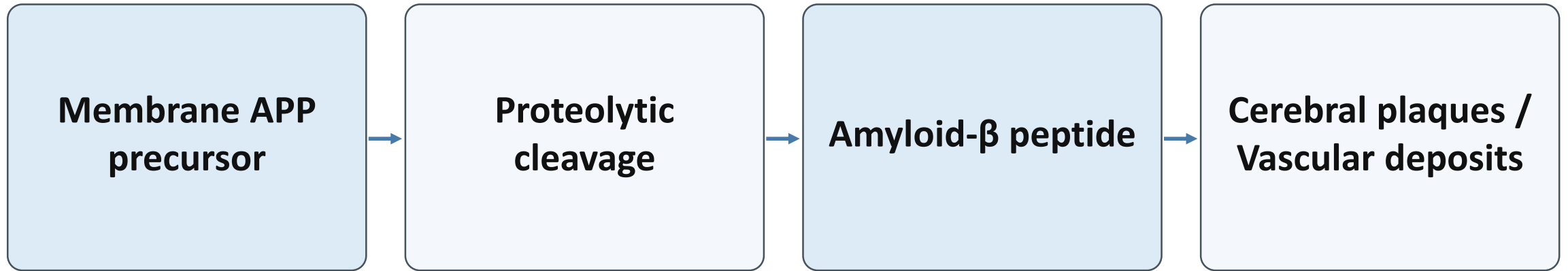
Long-term dialysis can allow precursor retention and tissue deposition.

Periarticular disease may produce carpal tunnel syndrome.

Interpretation

Dialysis-related amyloidosis illustrates failed systemic clearance.

Amyloid- β in the brain



Amyloid- β is derived from amyloid precursor protein (APP).

The source links these deposits to Alzheimer disease.

Amyloid- β illustrates organ-restricted biochemistry

Cerebral plaques and cerebral vessels can contain amyloid- β .

Its immediate precursor is a proteolytic product of APP.

It is not equivalent to systemic AL, AA or ATTR deposits.

Interpretation

Identical amyloid staining does not imply an identical source protein.

Local endocrine products can form amyloid

Some peptide hormones and endocrine-cell products are amyloidogenic.

These deposits are often microscopic and restricted to an organ or neoplasm.

The biochemical identity reflects the local secreted peptide.

Interpretation

Endocrine amyloid is a category of localized deposition, not a single protein.

Endocrine and organ-localized amyloid

Site / setting	Fibril designation	Precursor
Medullary thyroid carcinoma	ACal	Calcitonin
Type 2 diabetic islets	AIAPP	Islet amyloid polypeptide
Isolated atrial amyloid	AANF	Atrial natriuretic factor

These entries are taken from the textbook classification table.

Medullary thyroid carcinoma: ACal

Amyloid in the tumor stroma can derive from calcitonin.

The corresponding fibril designation in the source is ACal.

Local deposits provide a useful morphologic clue in this tumor.

Interpretation

Diagnostic significance depends on the tumor context; The deposit is not systemic AL.

Pancreatic islets: AIAPP

Amyloid in type 2 diabetes can occur in pancreatic islets.

Deposits are derived from islet amyloid polypeptide.

The category demonstrates how a local protein forms amyloid in situ.

Interpretation

AIAPP names the fibril identity; Diabetes is the associated setting.

Isolated atrial amyloidosis: AANF

Some atrial amyloid deposits derive from atrial natriuretic factor.

The source labels this localized type AANF.

It is biochemically distinct from transthyretin deposits in the heart.

Interpretation

The organ “heart” can contain several molecularly distinct amyloid proteins.

Localized nodules may still contain AL

Focal amyloid masses can arise in lung, larynx, skin, bladder or tongue.

Some show adjacent lymphocytes and plasma cells.

At least a subset consists of AL made by locally situated plasma cells.

Interpretation

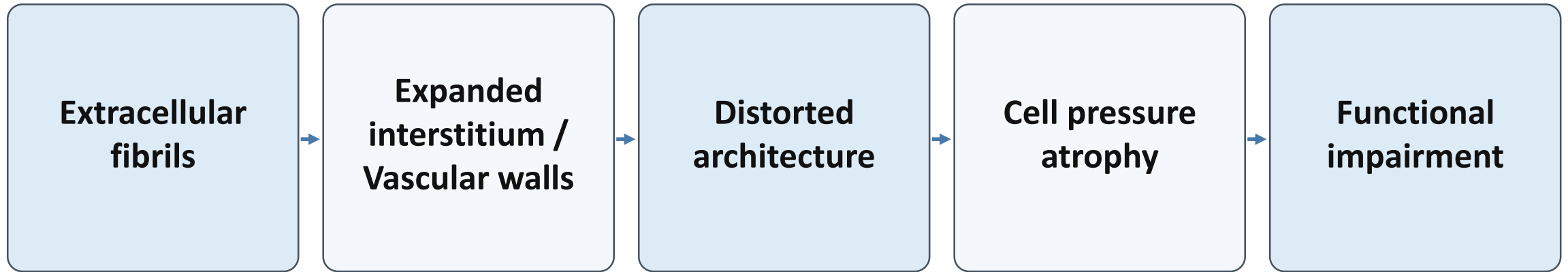
AL does not necessarily mean multi-organ systemic disease.

Classification: Selected uncommon forms

Fibril	Source / precursor	Representative setting
A β	APP-derived peptide	Alzheimer cerebral deposits
A β_2 m	β_2 -microglobulin	Long-term dialysis
ACal	Calcitonin	Medullary thyroid carcinoma
AIAPP	Islet amyloid polypeptide	Type 2 diabetic islets

Examples are not an exhaustive list of human amyloid fibril proteins.

How deposits produce organ dysfunction



The major injury mechanism described is architectural disruption.

Deposits cause tissue compromise without necessarily inducing local inflammation.

Pressure atrophy links structure to disease

Expanding material compresses cells and disrupts their tissue relationships.

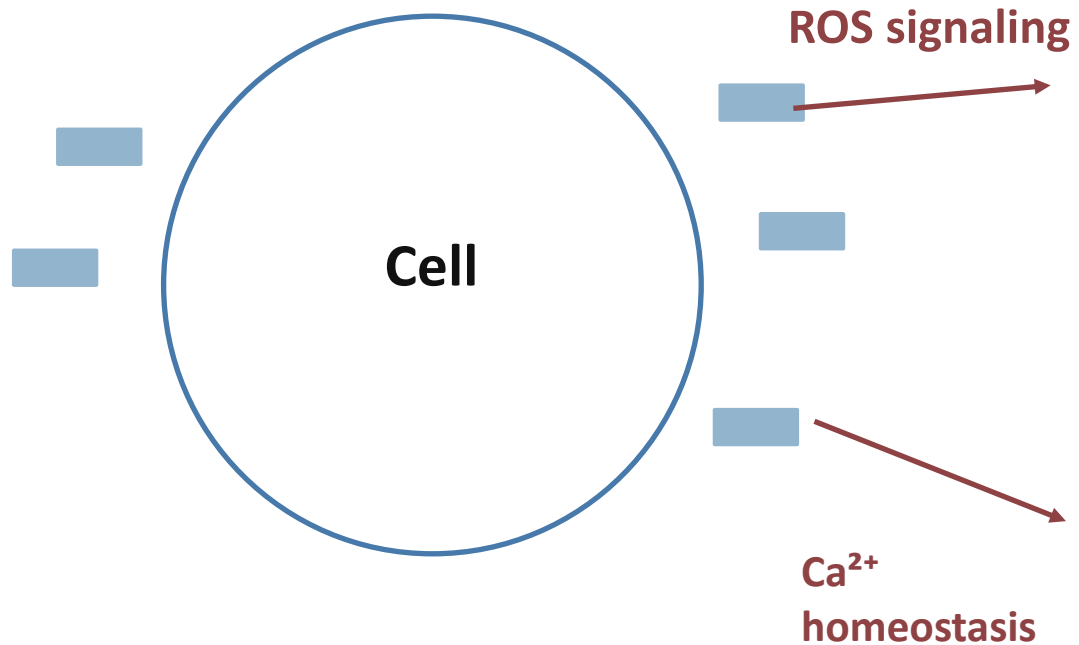
Vascular wall deposits can narrow lumens and compromise perfusion.

Progressive replacement of normal parenchyma reduces functional reserve.

Interpretation

Microscopic “acellular” material can cause profound organ dysfunction.

Deposits may also perturb cell signaling



Mechanistic interpretation

Some amyloidogenic proteins can induce reactive oxygen species production.

Altered calcium homeostasis may contribute to cellular dysfunction.

These as additional contributors beyond mass effect.

Renal versus cardiac consequences

Kidney

Deposits enlarge mesangium and glomerular capillary walls.

Progressive lumen obliteration impairs filtration.

Proteinuria and renal failure may follow.

Heart

Interstitial myocardial deposits separate and compress fibers.

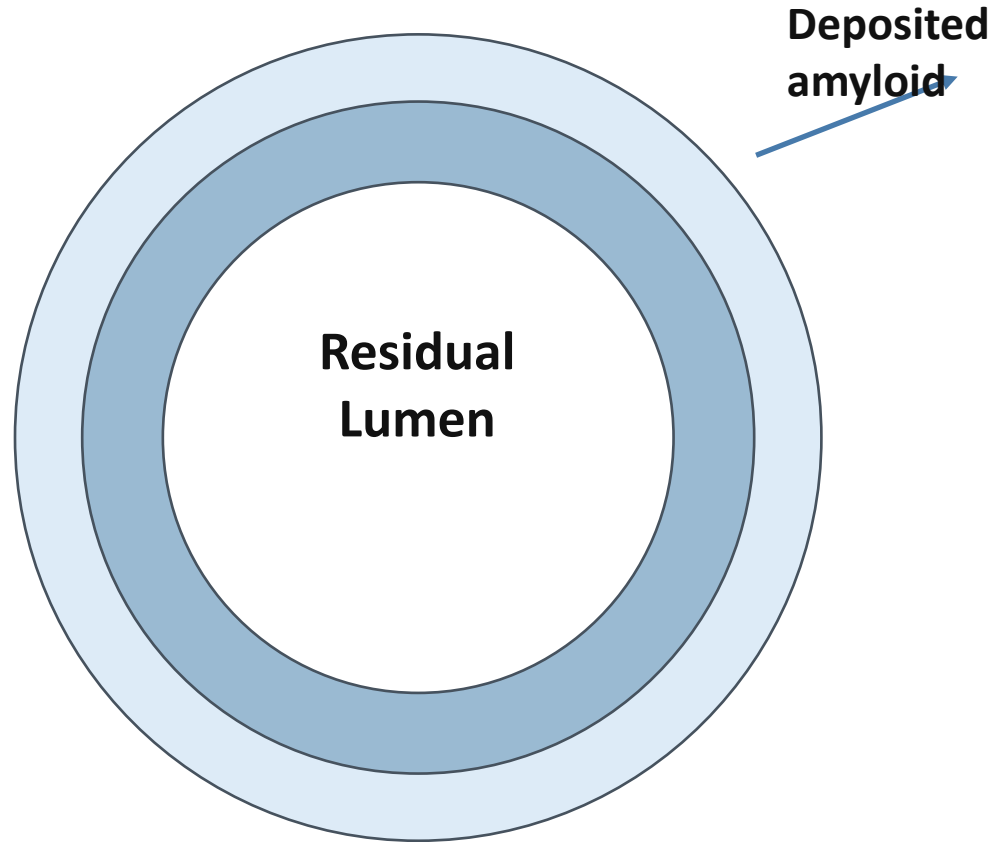
Subendocardial disease may affect conduction structures.

Heart failure or arrhythmia can result.

The same extracellular lesion causes organ-specific dysfunction.

Native tissue schematic: Vascular encroachment

Schematic vascular cross section



Mechanistic interpretation

Amyloid may deposit in vascular walls and perivascular connective tissue.

Increasing deposits reduce usable lumen and compress nearby cells.

This is an original conceptual diagram, not a histology specimen.

Morphology raises suspicion—not protein identity

Routine H&E shows amorphous eosinophilic extracellular material.

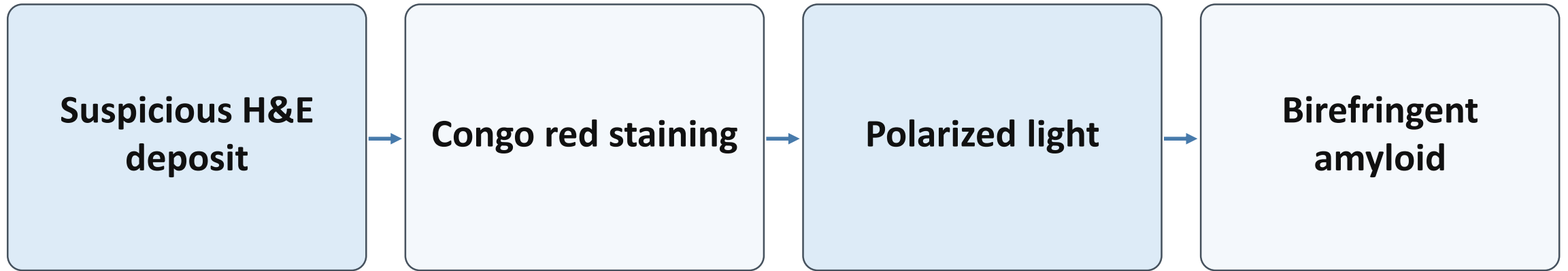
Collagen and fibrin may produce deceptively similar hyaline appearances.

A specific amyloid stain is required to establish the nature of the deposit.

Interpretation

Fibril typing is a second diagnostic question after deposit recognition.

Congo red: A structural recognition step



The source describes red/pink staining in brightfield and characteristic birefringence.

A common cross- β structure underlies the staining reaction across subtypes.

Detection and typing are distinct

Demonstrate amyloid

Appropriate tissue sample and histology.

Congo red and polarized microscopy.

Ultrastructure can show nonbranching fibrils.

Identify fibril protein

Type-specific immunohistochemistry may help.

Mass spectrometry can identify protein composition.

The biochemical answer guides clinical classification.

Congo red positivity alone does not identify AL versus AA versus ATTR.

Biopsy strategy follows organ involvement

Histologic demonstration in tissue is the diagnostic foundation.

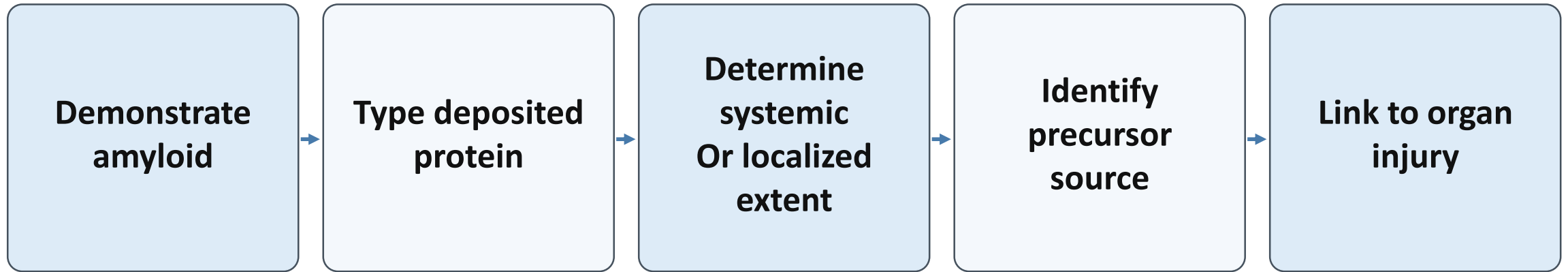
Kidney can be biopsied for renal manifestations; Other sites may be sampled.

Abdominal fat aspirate is a less invasive option for some systemic cases.

Interpretation

A negative limited sample cannot automatically exclude systemic amyloid.

Clinical classification sequence



Distribution, molecular identity and cause must be integrated.

An organ-based label alone cannot replace biochemical classification.

Same appearance, different molecular diagnoses

Evidence	Compatible interpretations
Congo red positive kidney biopsy	AL, AA or another systemic protein
Cardiac interstitial amyloid	ATTRwt, ATTRv, AL and others
Localized thyroid tumor amyloid	ACal in appropriate tumor context
Periarticular amyloid during dialysis	A β ₂ m is an important consideration

Examples teach diagnostic discrimination; They are not exclusive mappings.

Case: Monoclonal precursor

Clinical premise

Patient with systemic tissue amyloid and a monoclonal plasma-cell population.

AL is an important biochemical possibility.

The plasma-cell clone may produce amyloidogenic free light chains.

Confirmation still requires identifying the protein in the deposit.

Case: Persistent inflammatory stimulus

Clinical premise

Patient with long-standing active inflammatory arthritis and renal amyloid.

AA amyloidosis is mechanistically plausible.

Persistent IL-1/IL-6–linked signaling increases hepatic SAA.

The clinical history alone does not conclusively type the fibrils.

Case: Older adult with cardiac amyloid

Clinical premise

Older adult with predominantly cardiac amyloid and no specified inherited TTR variant.

ATTRwt belongs in the differential.

Normal transthyretin can form amyloid with aging.

AL and other possibilities must not be dismissed without typing.

Case: Affected family with neuropathy

Clinical premise

Several relatives develop peripheral or autonomic neuropathy with amyloid deposits.

Consider ATTRv and inherited amyloid disorders.

Specific TTR variants may show neural predilection.

Biochemical and genetic distinctions remain necessary.

Case: Isolated thyroid tumor deposit

Clinical premise

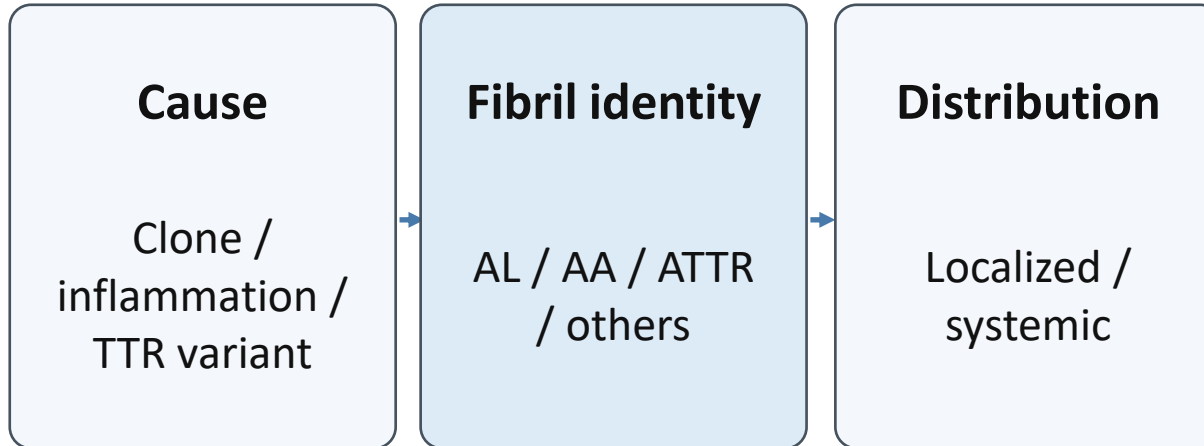
Medullary thyroid carcinoma includes stromal amyloid without evidence of generalized disease.

Calcitonin-derived ACal is a source-described form.

The amyloid is linked to a local endocrine product.

Do not interpret every tumor-associated amyloid deposit as systemic AL.

Integrated synthesis: Cause → fibril → distribution



Mechanistic interpretation

First identify the molecular precursor and amyloidogenic route.

Then establish where deposits occur and how tissue architecture is altered.

Finally connect the subtype to its defining etiologic setting.

Four distinctions to retain

Misfolded precursor $\neq$ mature deposited fibril.

Overproduced normal protein $\neq$ inherently amyloidogenic variant protein.

Systemic versus localized $\neq$ AL versus AA versus ATTR.

Amyloid detection $\neq$ amyloid protein typing.

Interpretation

These distinctions prevent the most important category errors in amyloidosis.

Reference

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

Amyloidosis — disease mechanisms, fibril chemistry and clinicopathologic forms.

Primary section: Pathogenesis and Classification of Amyloidosis.

See the adjacent AL, ATTR, AA and Other Types sections for the classification examples.