
Cholesterol and cholesterol esters

Intracellular accumulation • morphologic recognition • disease correlations

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Learning goals

- Explain how normal cells regulate cholesterol synthesis, uptake, esterification, and trafficking.
- Recognize foam cells, lipid vacuoles, and extracellular cholesterol clefts.
- Connect deposits with atherosclerosis, xanthomas, cholesterosis, and Niemann–Pick disease type C.
- Use tissue location and molecular mechanism to build a pathologic differential.

Intracellular accumulation is a metabolic lesion

- Normal molecules may accumulate when uptake, synthesis, handling, or removal becomes imbalanced.
- Deposits can be innocuous or can disturb organelle function and provoke tissue injury.
- Material may be in the cytosol, lysosomes, or other cell compartments.

Accumulation is an observation; The mechanism must be inferred from content and location.

Four broad routes to intracellular deposits

Impaired handling

Normal material is not effectively removed or transported.

Endogenous abnormal product

Defective folding, transport, or secretion causes retention.

Blocked degradation

Enzyme deficiency prevents normal metabolic clearance.

Indigestible material

External particles are retained because disposal mechanisms are absent.

Lipids are not one histologic category

Triglycerides

Steatosis: Classically liver parenchymal cells.

Cholesterol / esters

Foam cells in several vascular and extravascular lesions.

Phospholipids

Myelin figures may occur during cell injury and necrosis.

Cells require cholesterol without storing excess

- Cholesterol is a normal constituent needed for cell-membrane synthesis.
- Most cells regulate its availability and prevent visible intracellular accumulation.
- Prominent vacuolation therefore signals an altered balance or trafficking defect.

The physiological need is not the same as a pathologic excess.

Free cholesterol versus cholesterol esters

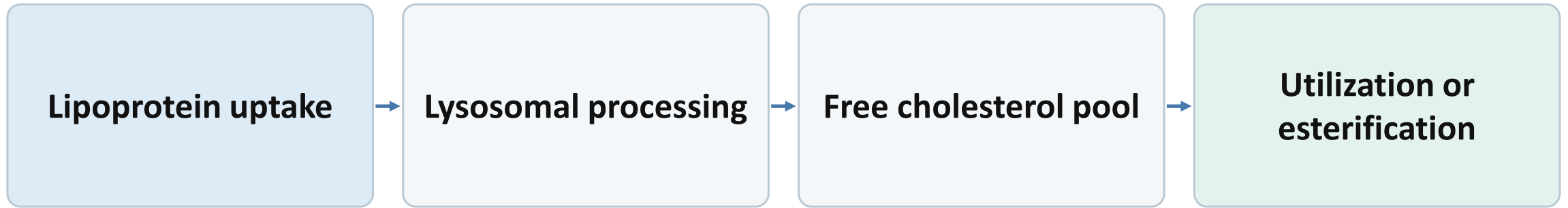
Free cholesterol

Used for membrane synthesis and regulates cellular cholesterol homeostasis.

Cholesteryl esters

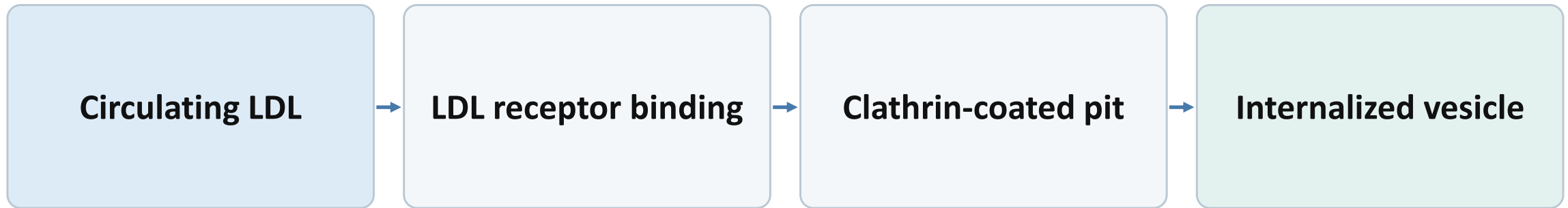
Esterified storage form produced when intracellular cholesterol is abundant.

Cholesterol homeostasis is a flux problem



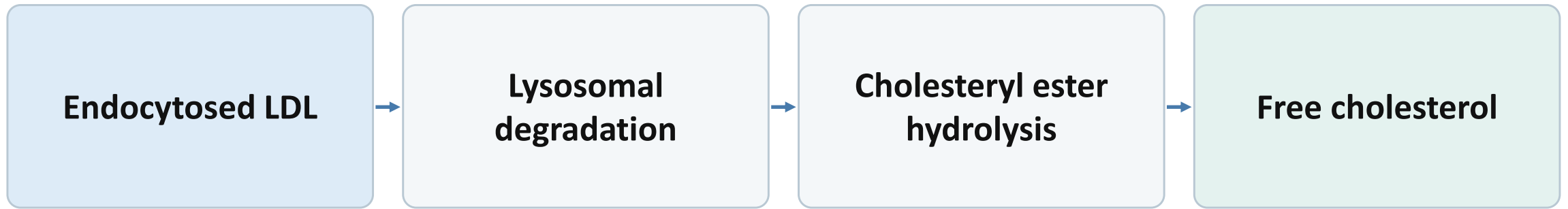
Feedback also reduces synthesis and receptor-mediated influx when cholesterol rises.

LDL receptors initiate a regulated uptake pathway



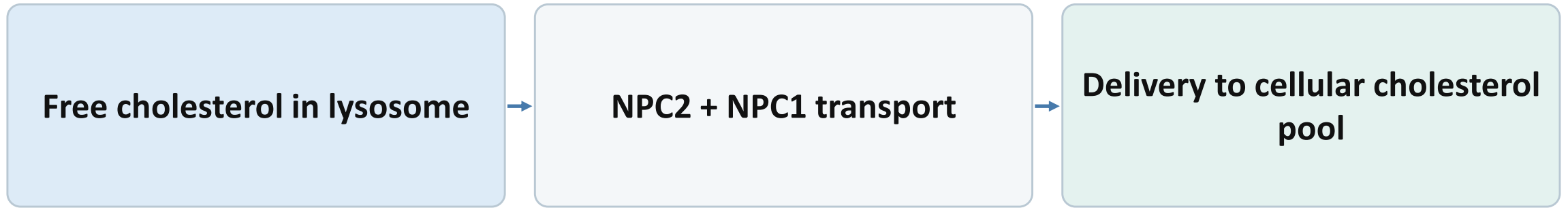
High-affinity LDL receptors operate in many cell types; Hepatic clearance is prominent.

Lysosomes release free cholesterol from LDL



The apoprotein component is degraded, and esterified cholesterol is converted to free cholesterol.

NPC1 and NPC2 permit lysosomal egress



NPC2 is soluble; NPC1 is membrane-associated. A transport defect results in lysosomal retention.

Intracellular cholesterol restrains synthesis



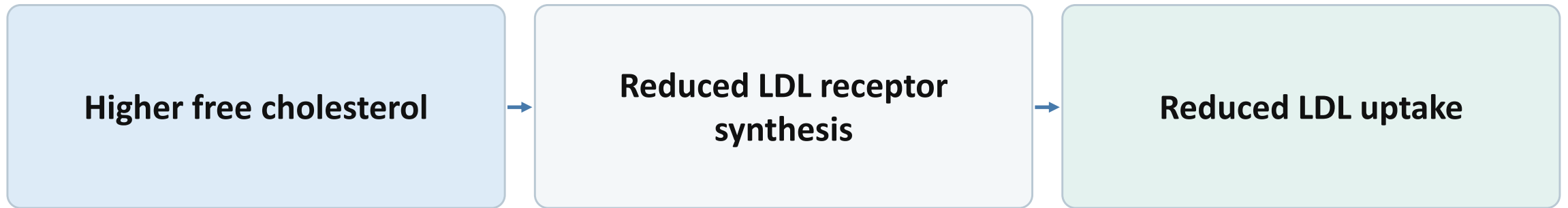
A homeostatic negative-feedback response to excess available cholesterol.

Excess cholesterol is directed to esterification



ACAT = acyl-coenzyme A:cholesterol acyltransferase.

Cholesterol suppresses LDL receptor production



Limiting entry is another protection against excessive intracellular cholesterol.

PCSK9 also modulates receptor recycling



PCSK9 binding promotes loss of endocytosed receptors rather than their recycling.

Four safeguards act on cholesterol balance

Synthesis

Feedback reduces HMG-CoA reductase activity.

Storage

ACAT converts excess free cholesterol to esters.

Entry

LDL receptor synthesis is reduced.

Recycling

PCSK9 promotes LDL receptor degradation.

Why normal regulation can be overwhelmed

- Excess input, altered intracellular processing, or impaired egress can exceed compensatory control.
- The same lipid can therefore accumulate in different cells by different routes.
- Disease identification needs anatomy and cell lineage—not lipid appearance alone.

Synthesis across these textbook sections.

Cholesterol accumulation has recognizable settings

Atheroma

Intimal macrophages and smooth muscle cells in large arteries.

Xanthoma

Foamy macrophage clusters in skin or tendons.

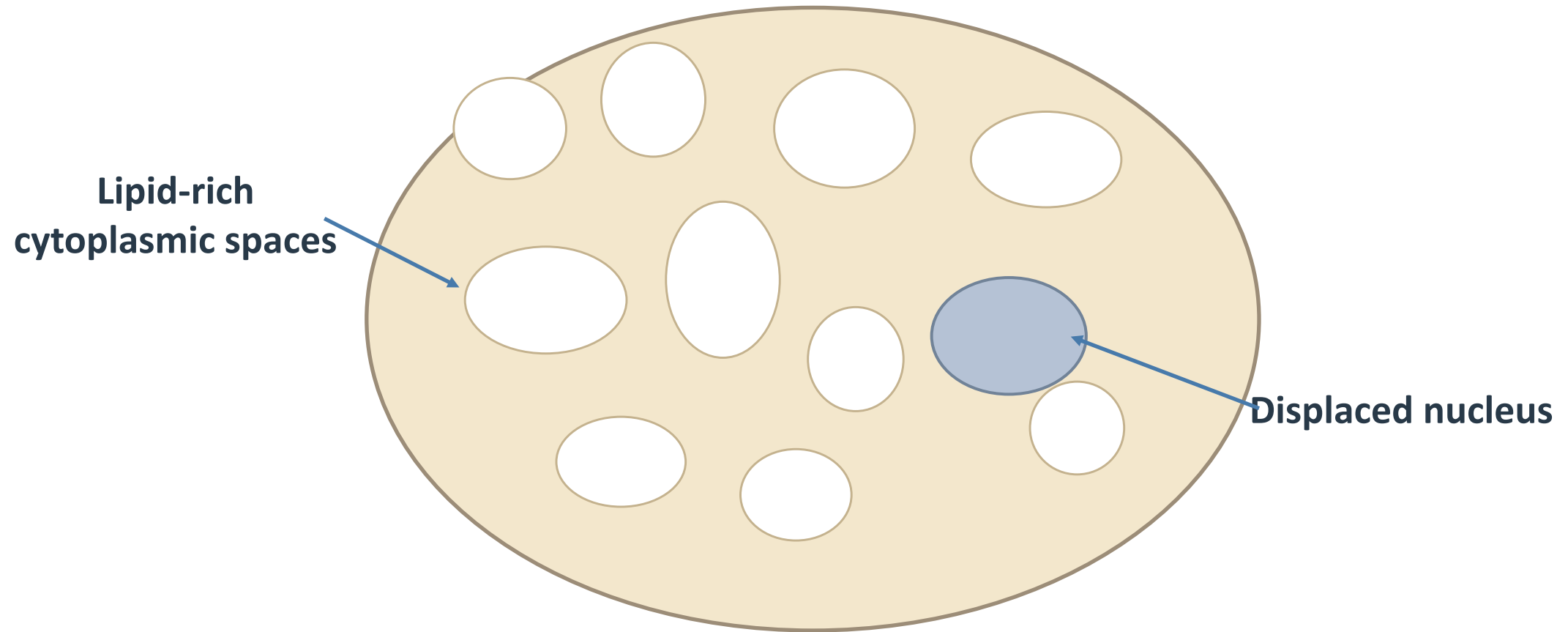
Cholesterolosis

Foam cells in gallbladder lamina propria.

Niemann–Pick C

Defective lysosomal export; Multiple organs affected.

A foam cell is a morphology, not a diagnosis



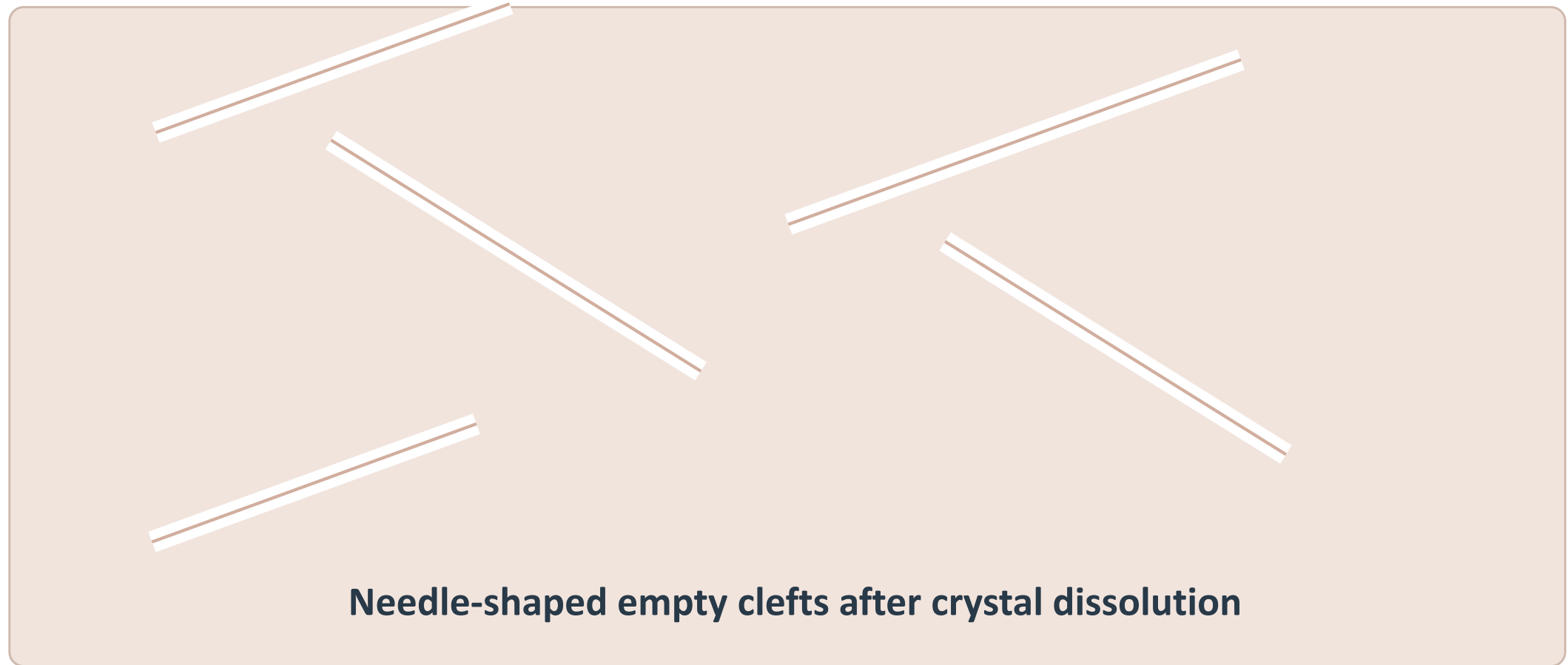
Schematic — not a histologic specimen

Cytoplasmic vacuoles require interpretation

- A clear-appearing cytoplasmic space alone does not identify its chemical content.
- In this textbook setting, cholesterol and cholesteryl ester accumulation is associated with foamy vacuolated cells.
- Tissue site, architecture, accompanying inflammation, and clinical context refine the diagnosis.

Morphologic interpretation—not a claim that a single routine stain is diagnostic for cholesterol.

Extracellular cholesterol may leave clefts



Schematic — crystals may be removed by routine tissue processing

Intracellular lipid and extracellular clefts differ

Intracellular

Pale vacuoles occupy foam-cell cytoplasm.

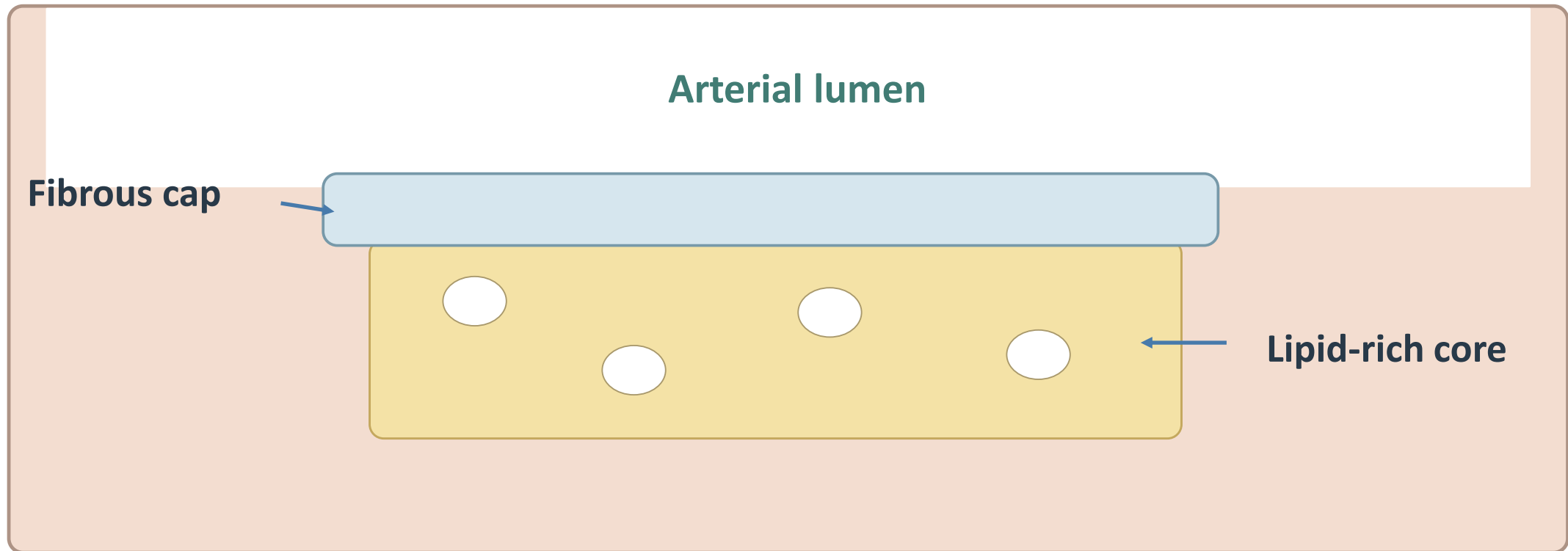
Extracellular

Released lipids may crystallize;
Dissolution during processing leaves
needle-like clefts.

Where are the foam cells located?

Tissue site	Cellular location	Likely teaching context
Artery	Intimal macrophages / SMCs	Atherosclerosis
Skin or tendon	Subepithelial / tendinous macrophages	Xanthoma
Gallbladder	Lamina propria macrophages	Cholesterolosis
Multiple organs	Lysosomal cholesterol accumulation	Niemann–Pick C

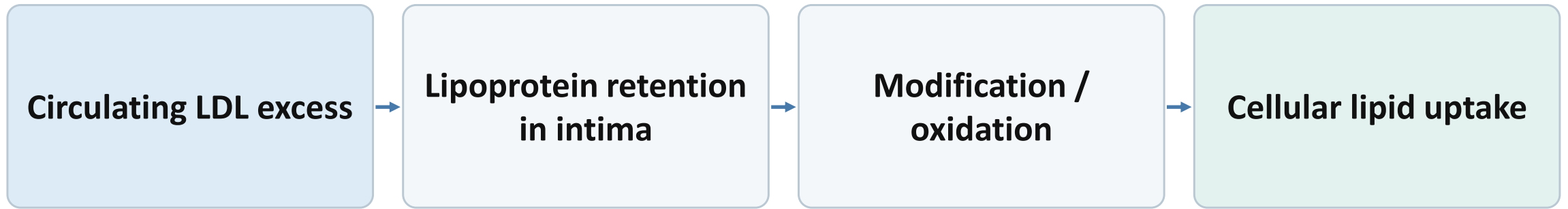
The artery is a major setting for cholesterol storage



Atheromas arise within the arterial intima

- Large arteries and the aorta develop intimal accumulations of lipid-laden macrophages and smooth muscle cells.
- Aggregates form grossly yellow, cholesterol-rich plaques.
- Intimal localization is central to recognizing atheromatous disease.

Hypercholesterolemia promotes intimal lipid entry



Modified lipoproteins are especially important in building macrophage and smooth muscle foam cells.

Modified LDL differs from ordinary receptor uptake

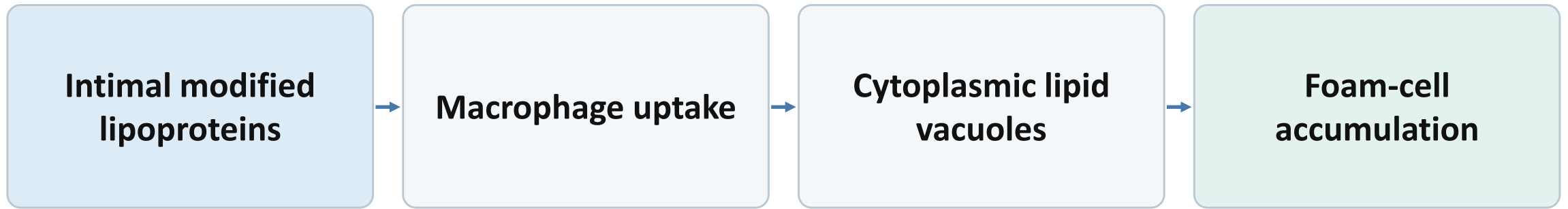
Physiologic LDL transport

LDL receptors internalize particles;
Feedback limits further influx.

Intimal modified LDL

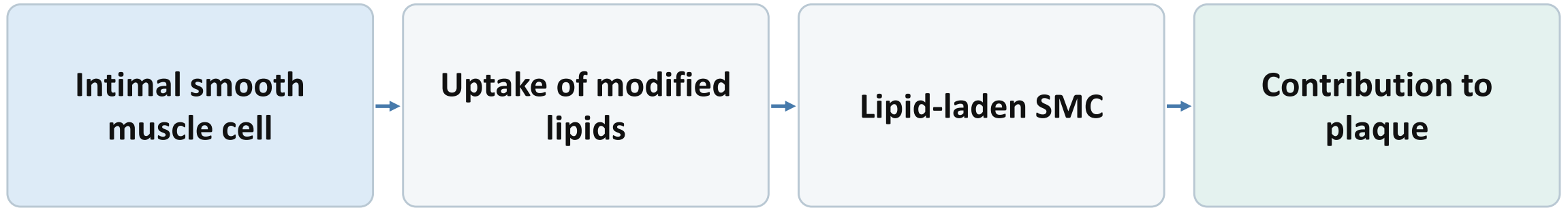
Scavenger-related uptake by lesional
cells contributes to persistent lipid
loading.

Macrophages become foam cells



Chronic modified-lipoprotein ingestion produces the characteristic foamy phenotype.

Smooth muscle cells can also become foam cells



Do not equate every plaque foam cell with macrophage lineage.

Fatty streaks contain foamy macrophages

- Early lesions consist mainly of lipid-laden macrophages.
- Grossly they are yellow macules or linear streaks.
- They generally cause little or no disturbance of blood flow at this stage.

Fatty streak is not synonymous with mature plaque

Fatty streak

Predominantly foamy macrophages;
Limited luminal effect.

Atheromatous plaque

Fibrous cap, cellular elements,
extracellular matrix, and lipid-rich
necrotic core.

A mature atheroma contains four component classes

Cells

Macrophages, smooth muscle cells, T lymphocytes.

Extracellular matrix

Collagen, proteoglycans, elastic fibers.

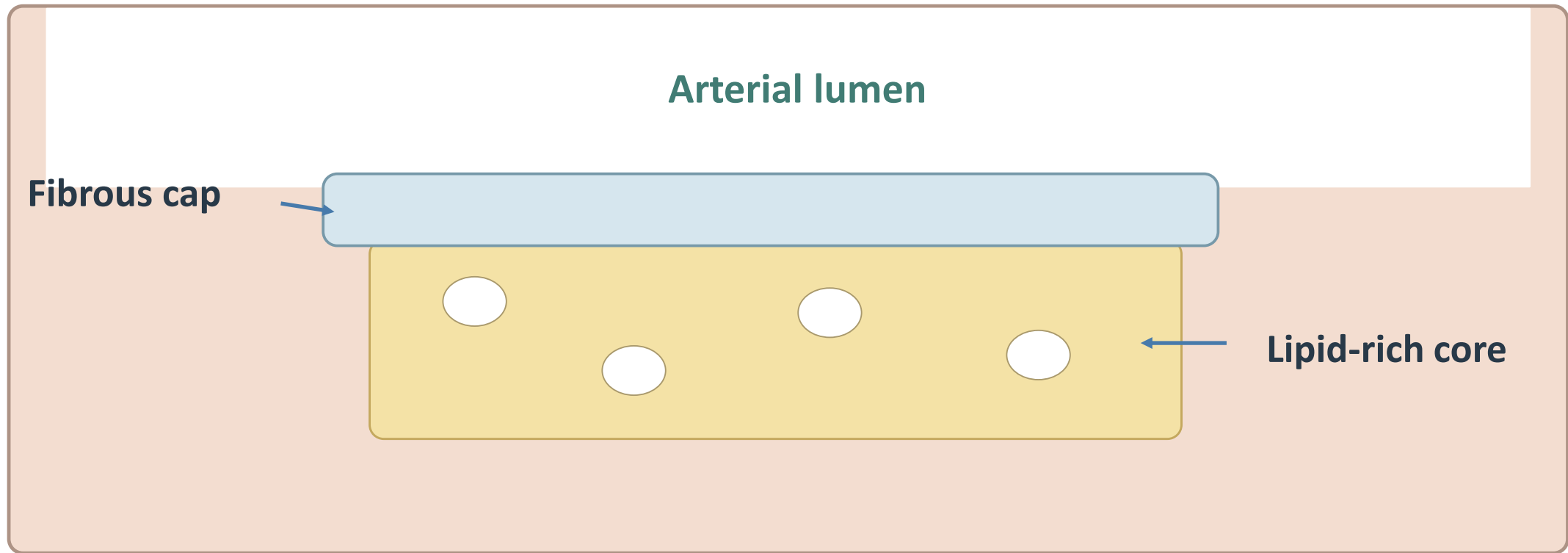
Lipids

Intracellular and extracellular cholesterol-rich material.

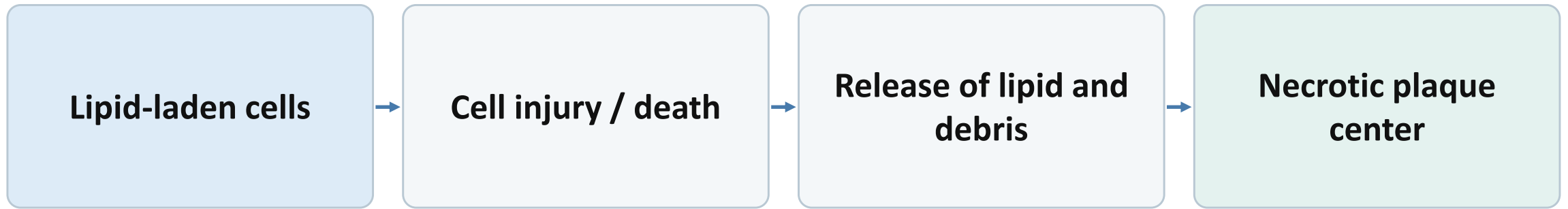
Mineral

Calcification may appear in advanced plaques.

The fibrous cap overlies the lipid-rich core

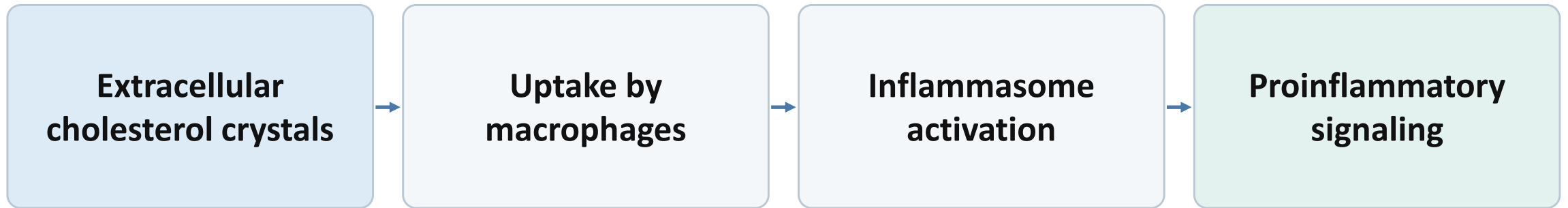


Foam-cell death enlarges the necrotic core



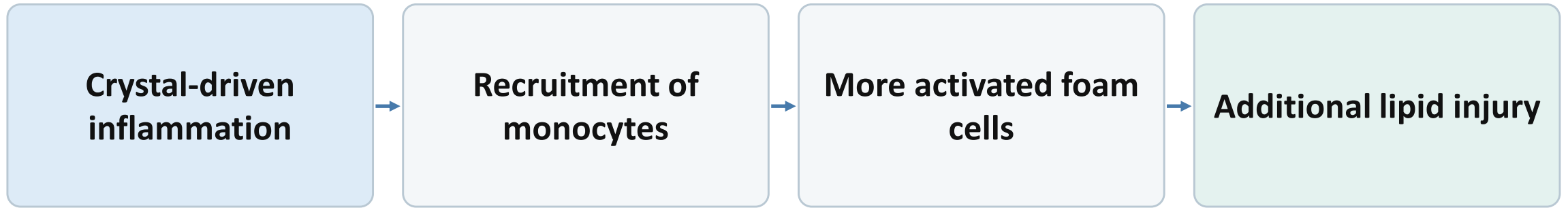
This provides a route from cellular storage to extracellular atheromatous material.

Cholesterol crystals can amplify inflammation



Crystal sensing with IL-1–associated local inflammation.

Inflammation reinforces lipid accumulation



Atherogenesis is a sustained inflammatory response, not passive lipid deposition.

Fibrous matrix and inflammatory injury oppose

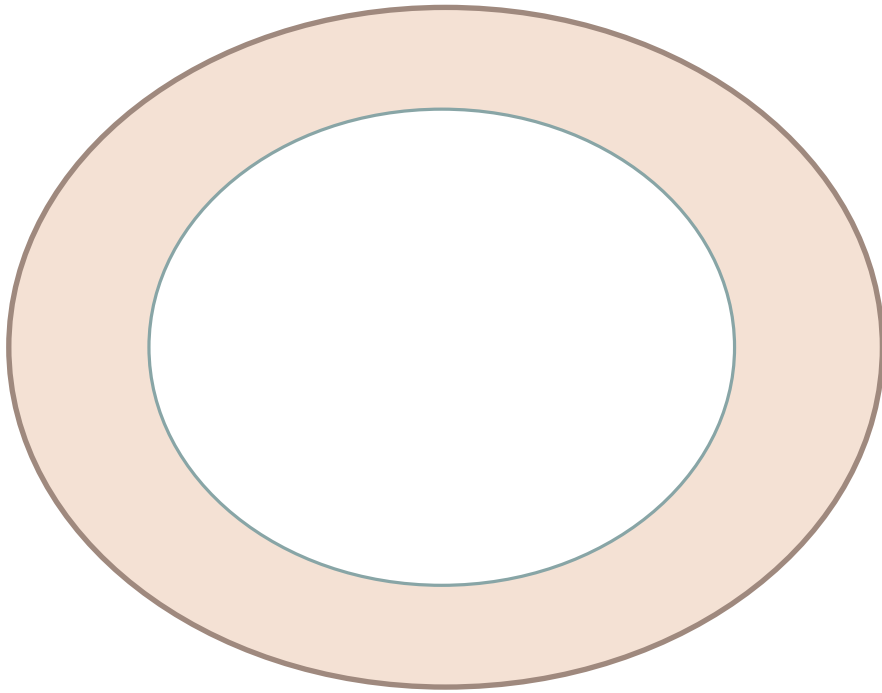
Matrix deposition

SMCs synthesize collagen and matrix;
Cap may be stabilized.

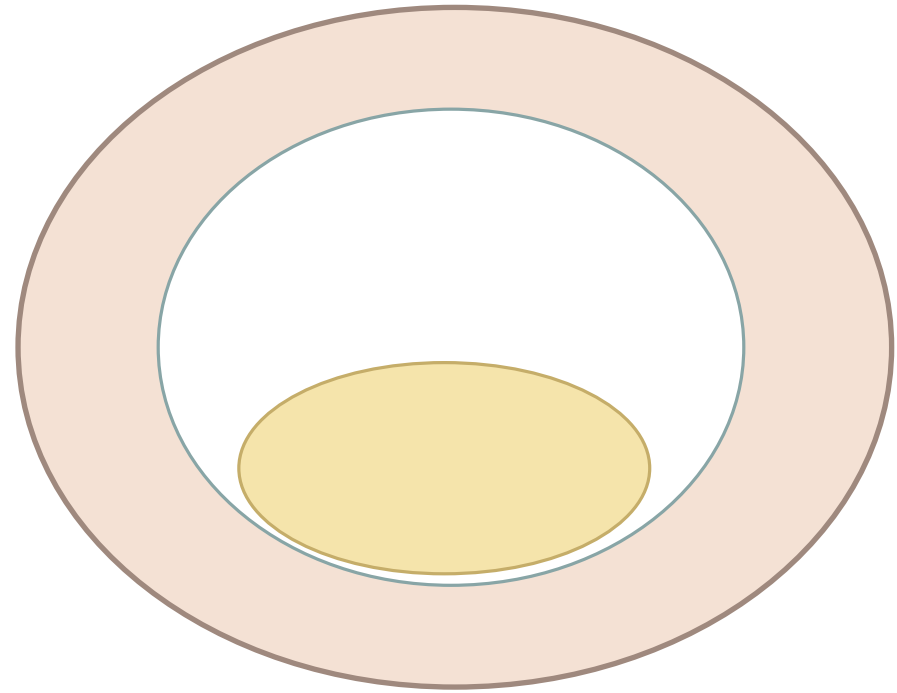
Matrix breakdown

Inflammatory cell products can weaken
cap and increase rupture susceptibility.

Plaque progression can narrow the lumen



Unobstructed lumen



Plaque encroaches on lumen

Advanced plaques have several complications

Thrombosis

Surface rupture or erosion can expose thrombogenic material.

Intraplaque bleeding

May abruptly increase plaque volume.

Atheroembolism

Dislodged plaque debris can enter distal circulation.

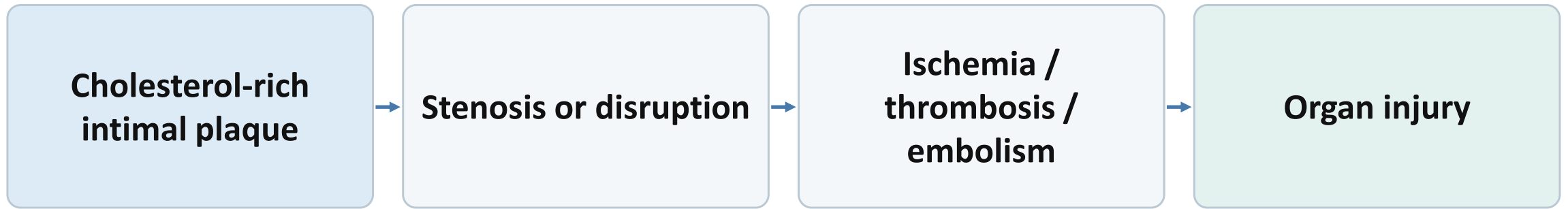
Wall weakening

Medial injury can favor aneurysmal dilation.

Cholesterol clefts may identify atheromatous debris

- Large crystal spaces in plaque cores reflect processing loss of cholesterol crystals.
- Clefts can persist among necrotic debris even when many viable foam cells have disappeared.
- Distribution in the arterial intima anchors the interpretation as atheromatous.

Clinical damage is downstream of the plaque lesion



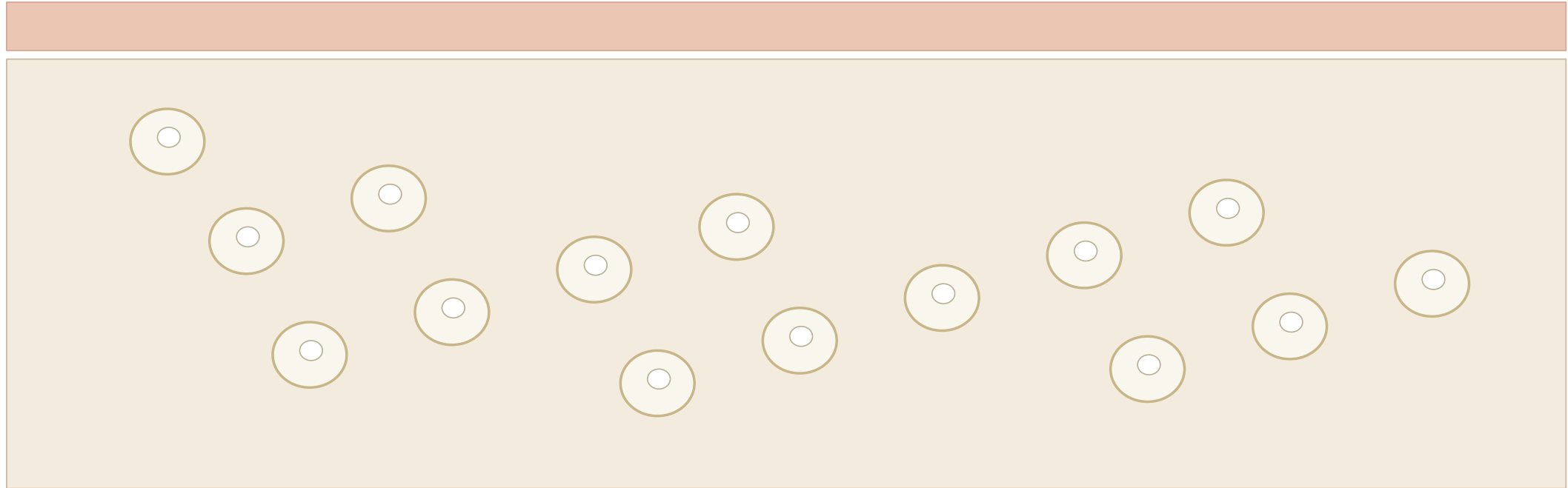
Clinical outcomes depend on vascular distribution and plaque complications.

Xanthoma is a tissue mass of lipid-laden cells

- Aggregates of macrophages acquire conspicuous cholesterol-rich cytoplasmic vacuoles.
- Clusters form nodular or tumorous deposits in skin or tendons.
- The lesion is a sign of lipid accumulation, not evidence of neoplastic macrophage proliferation.

Skin and tendons are classic xanthoma sites

Surface epithelium



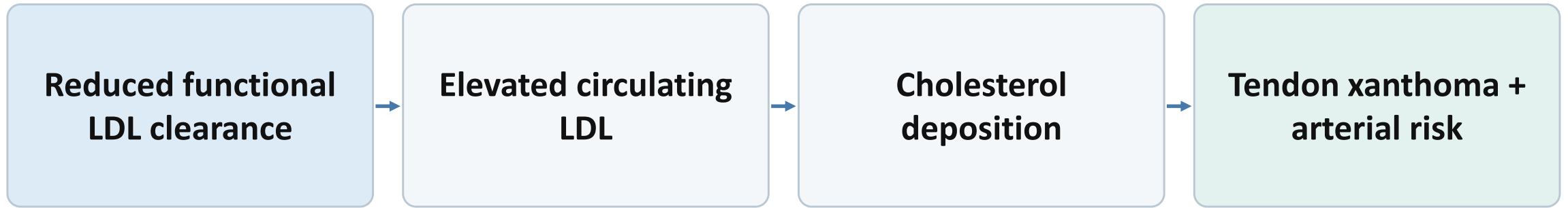
Subepithelial connective tissue / tendon

Schematic distribution of lipid-laden macrophages

Xanthomas can accompany different lipid disorders

- The chapter associates xanthomas with both hereditary and acquired hyperlipidemic states.
- Clinical evaluation should distinguish tissue deposition from the underlying circulating lipoprotein abnormality.
- A localized histologic pattern does not itself define which lipoprotein defect is present.

Familial hypercholesterolemia links LDL and tendons



The source links defective hepatic LDL uptake with tendon deposits and accelerated atherosclerosis.

Xanthoma and atheroma share cells, not anatomy

Xanthoma

Subepithelial connective tissue or tendon; Localized foamy macrophage mass.

Atheroma

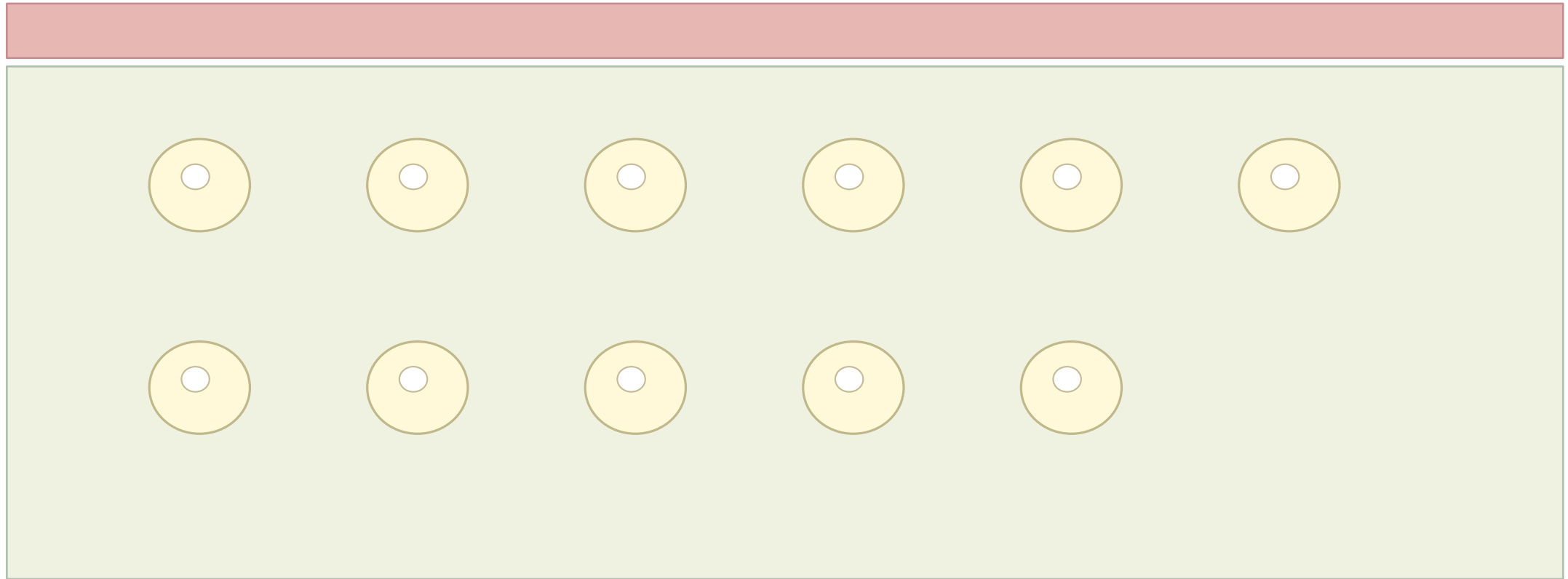
Arterial intima; Foamy cells plus matrix, necrotic core, and potential luminal complications.

Cholesterolosis has a distinct tissue location

- Cholesterol-laden macrophages accumulate focally in the gallbladder lamina propria.
- The mucosal compartment—not the arterial intima or tendon—is the diagnostic context.
- The mechanism of accumulation is unknown.

Recognize lamina propria foamy macrophages

Gallbladder mucosal epithelium



Lamina propria

Unknown pathogenesis must remain unknown

Established observation

Focal cholesterol-laden macrophages in gallbladder lamina propria.

Not established in this source

A specific causal route explaining why macrophages accumulate cholesterol here.

Location discriminates two foamy processes

Feature	Cholesterolosis	Atherosclerosis
Compartment	Gallbladder lamina propria	Arterial intima
Cell emphasis	Cholesterol-laden macrophages	Macrophages and SMCs
Characteristic structure	Mucosal focal accumulations	Atheromatous plaque
Mechanism in Ch. 2	Unknown	Lipid uptake, crystal injury

Niemann–Pick C is an inherited trafficking defect

- This lysosomal storage disease results from pathogenic variants in NPC1 or NPC2.
- The primary lesion is failure of nonenzymatic cholesterol transport out of lysosomes.
- Cholesterol consequently accumulates across multiple organs.

The short Chapter 2 description says “enzyme”; Chapter 5 clarifies that NPC1/2 are transport proteins, not a hydrolase deficiency.

NPC1 and NPC2 have complementary locations

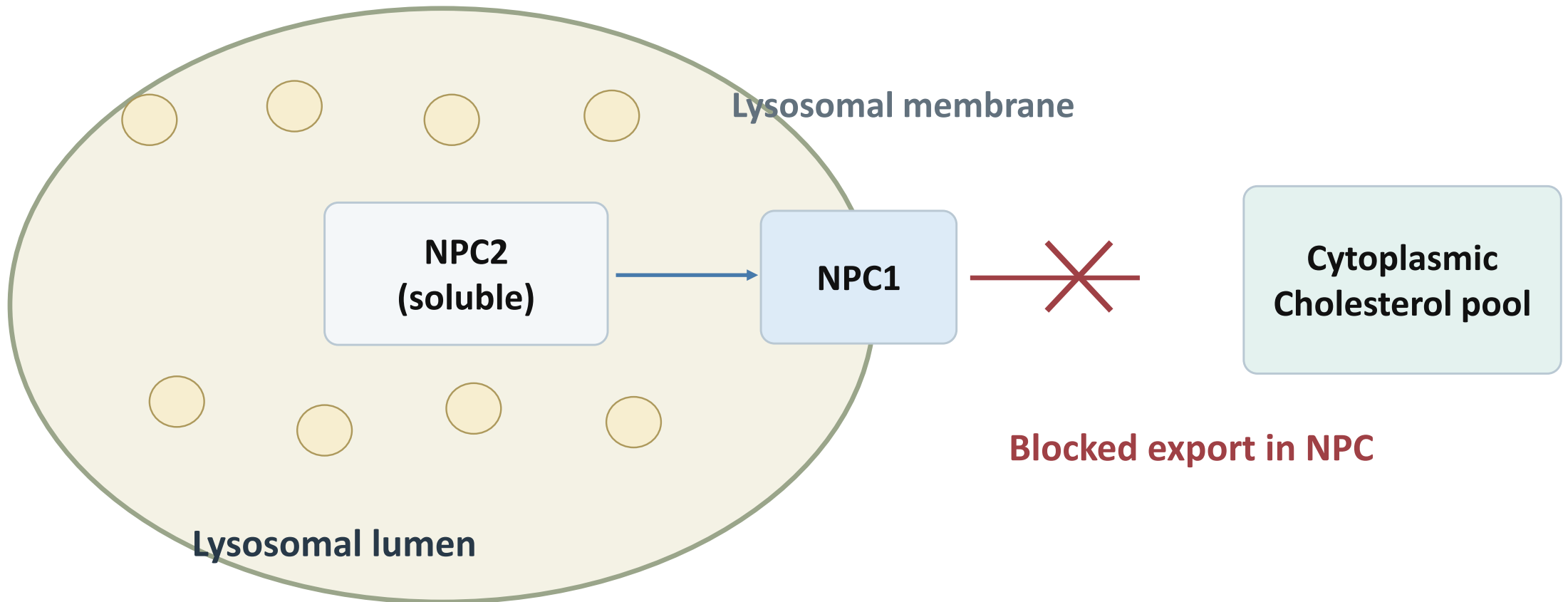
NPC1

Membrane-associated protein involved
in lysosomal cholesterol export.

NPC2

Soluble lysosomal protein participating
in free cholesterol transport.

Failed export causes lysosomal retention



Schematic of transport failure: Cholesterol remains within lysosomes

NPC differs from enzyme-deficiency storage disease

NPC type C

Defective intracellular trafficking of free cholesterol.

Niemann–Pick types A/B

Deficient acid sphingomyelinase with sphingomyelin accumulation.

NPC affects visceral and neural systems

- Marked clinical heterogeneity, including fetal and neonatal presentations.
- The more usual chronic form involves progressive neurologic deterioration.
- A cellular cholesterol-trafficking disorder can therefore present as a multisystem disease.

Neurologic clues to NPC type C

Ataxia

Loss of coordinated movement.

Vertical gaze palsy

Supranuclear limitation of vertical eye movements.

Dystonia / dysarthria

Abnormal muscle tone and impaired articulation.

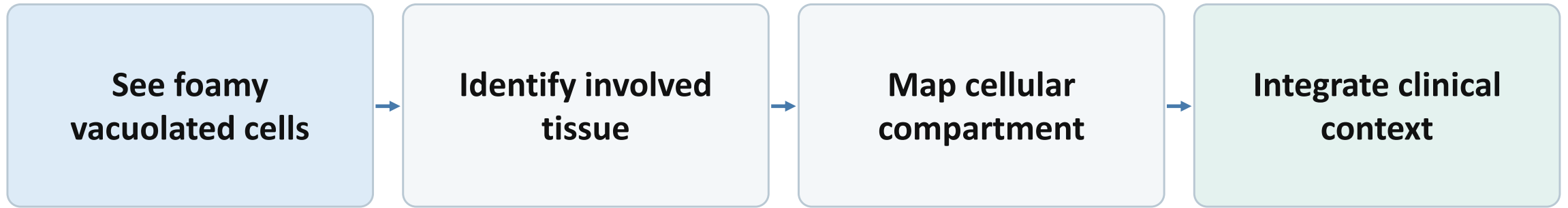
Psychomotor regression

Loss of previously acquired abilities.

Inherited NPC and acquired deposits should separate

Dimension	Niemann–Pick C	Atheroma / xanthoma
Primary abnormality	NPC1/2 cholesterol transport	Lipid loading in local tissue
Subcellular emphasis	Lysosomal retention	Foam-cell lipid storage
Tissue distribution	Multiorgan	Artery / skin / tendon
Clinical emphasis	Progressive neurologic disease	Vascular or localized deposits

A pathology differential begins with location



The same cytologic appearance is shared by multiple cholesterol-associated disorders.

Interpret a cholesterol-associated lesion systematically

Observation	Interpretation	What it does NOT prove
Foamy macrophages	Intracellular lipid accumulation	A single cause or lipid class
Arterial intimal plaque	Supports atheromatous process	That all foam cells are macrophages
Needle-like clefts	Suggests extracellular crystals	That crystals remain in processed tissue
Multisystem storage	Raises inherited trafficking defect	Specific gene without confirmation

Case: A yellow lesion in an artery

A raised, yellow-tan intimal arterial lesion contains foamy macrophages, smooth muscle cells, a fibrous cap, and empty needle-like spaces.

Which stored material and process best integrate these findings?

Reasoned interpretation: Cholesterol/cholesteryl ester accumulation in an atheromatous plaque; Released crystals leave clefts.

Case: Tendon nodules and elevated LDL

Tendon nodules contain aggregates of foamy macrophages. The clinical history suggests a hereditary disorder of LDL clearance.

What lesion is present, and what vascular disease should be considered?

Reasoned interpretation: Tendon xanthomas; Inherited hypercholesterolemia can be linked to accelerated atherosclerosis.

Case: Vacuolated cells in the gallbladder

A gallbladder specimen shows focal groups of lipid-laden macrophages in the mucosal lamina propria.

What is the morphologic term? Can the pathogenesis be asserted?

Reasoned interpretation: Cholesterolosis; The source explicitly describes its accumulation mechanism as unknown.

Case: Progressive neurologic decline with storage

A multisystem lipid-storage disorder is associated with ataxia, vertical supranuclear gaze palsy, and psychomotor regression.

What trafficking pathway and genes should be considered?

Reasoned interpretation: Niemann–Pick type C, involving NPC1 or NPC2 and impaired lysosomal free-cholesterol export.

Compare the four primary disease settings

Entity	Main site	Distinctive clue
Atherosclerosis	Large arterial intima	Foam cells, lipid core, crystal clefts
Xanthoma	Skin / tendon	Mass of foamy macrophages
Cholesterolosis	Gallbladder lamina propria	Focal foamy macrophages
Niemann–Pick C	Multiple organs / lysosomes	NPC1/2 transport failure

Avoid three common diagnostic shortcuts

- “Foam cell” describes cytoplasm; It does not specify tissue, disease, or cell lineage.
- “Cholesterol crystal” and “cholesterol cleft” refer to related—but not identical—states.
- Niemann–Pick type C is a trafficking disorder; It must not be confused with acid sphingomyelinase deficiency.

Core concepts to retain

Homeostasis

Cells control uptake, synthesis, storage, and transport.

Morphology

Intracellular foam cells differ from extracellular cholesterol clefts.

Location

Artery, tendon/skin, gallbladder, and lysosome provide diagnostic context.

Mechanism

Cholesterol crystals can provoke inflammation; NPC defects impair export.

Primary teaching references

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th edition (2026).
- Chapter 2, “Intracellular Accumulations,” pp. 56–58; emphasis on cholesterol and cholesterol esters, p. 57.
- Chapter 5, cellular cholesterol metabolism, familial hypercholesterolemia, and Niemann–Pick disease type C.
- Chapter 11, atherosclerosis: lipid accumulation, foam cells, inflammasome, and plaque morphology.

All diagrams are native, original schematics—not reproduced textbook micrographs.