

Disorders Associated With Defects in Receptor Proteins

Familial hypercholesterolemia as a model of impaired receptor-mediated transport

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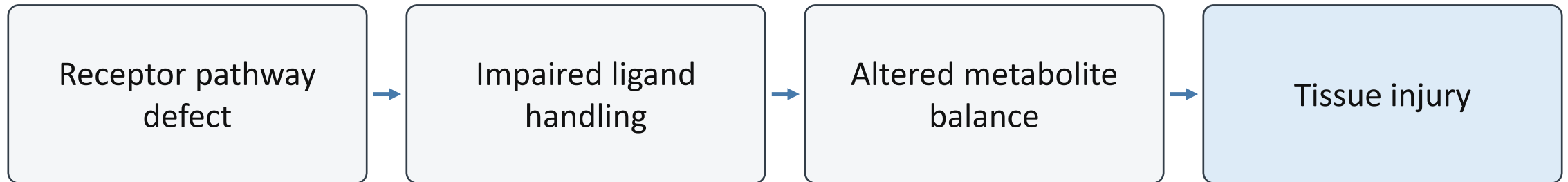
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Learning objectives

- Explain why failure of an LDL receptor pathway elevates circulating cholesterol.
- Trace normal LDL formation, hepatic uptake, receptor recycling, and feedback control.
- Distinguish defects in LDLR, ApoB, and PCSK9 from one another.
- Classify LDLR defects by the disrupted stage of receptor function.
- Link molecular defects to xanthomas, atherosclerosis, and receptor-directed therapies.

Receptor defects: A disease mechanism



Familial hypercholesterolemia illustrates how a transport defect becomes vascular disease.

The receptor pathway must do more than bind

Recognition

A ligand must bind a functioning extracellular receptor domain.

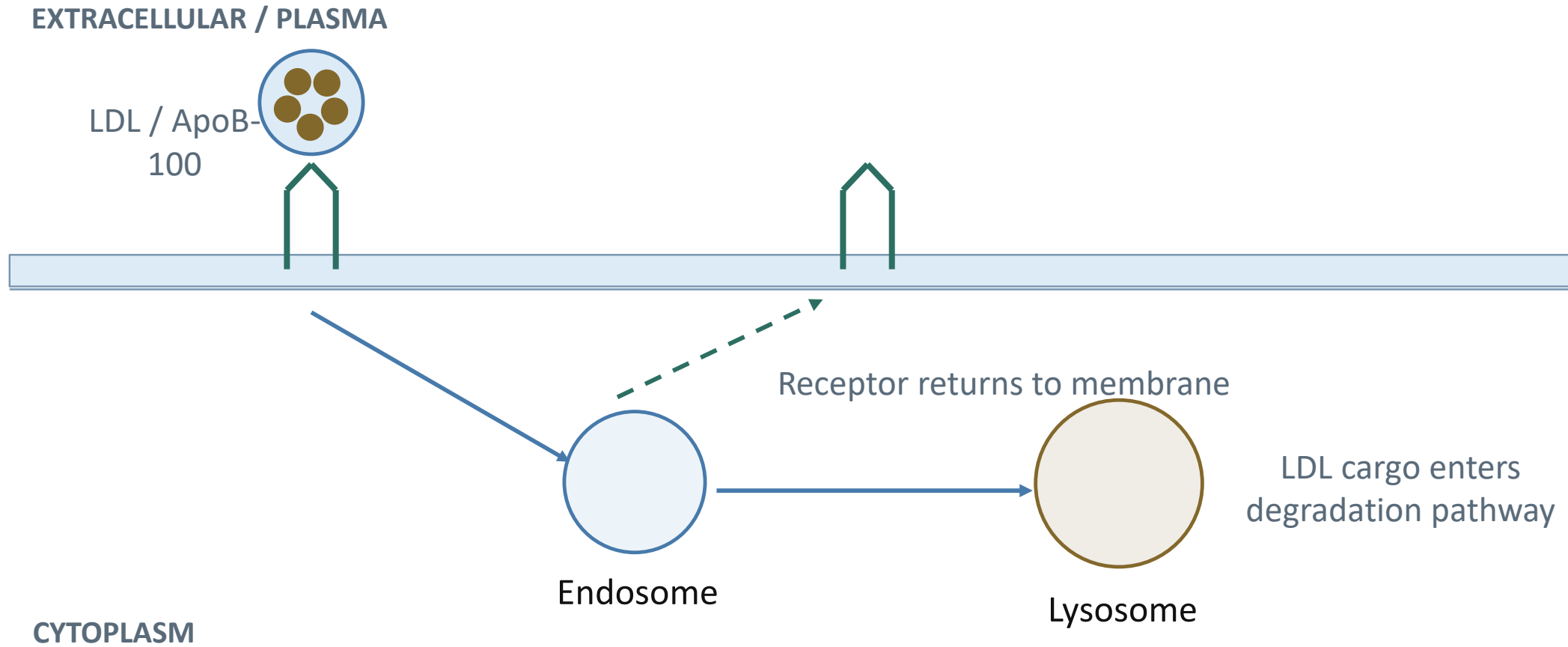
Transport

Receptors and ligands must enter the appropriate intracellular pathway.

Recovery

Receptors are normally returned to the cell surface for repeated use.

LDL clearance is a multistep cellular process



Familial hypercholesterolemia: Core defect

Reduced hepatic clearance of plasma LDL

LDL persists in the circulation; Chronically increased plasma cholesterol accelerates atherosclerosis and produces cholesterol-rich tissue deposits.

Three genes converge on the LDL receptor pathway

LDLR

Encodes the LDL receptor itself. Mutations reduce receptor number or functional efficiency.

APOB

Encodes ApoB-100, the LDL particle ligand. Mutations reduce receptor binding.

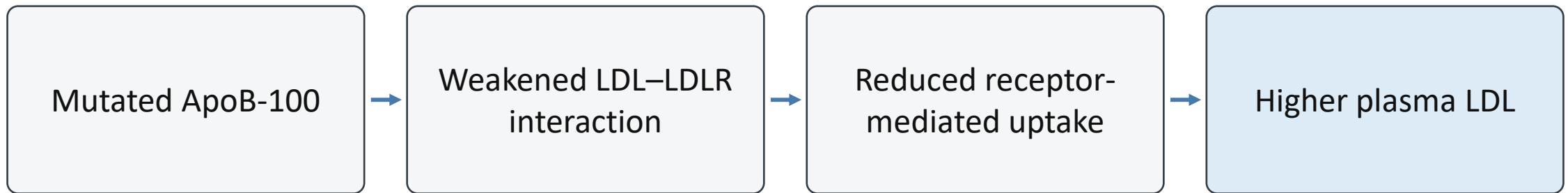
PCSK9

Activating variants accelerate LDL receptor degradation and limit recycling.

LDLR: The dominant genetic category

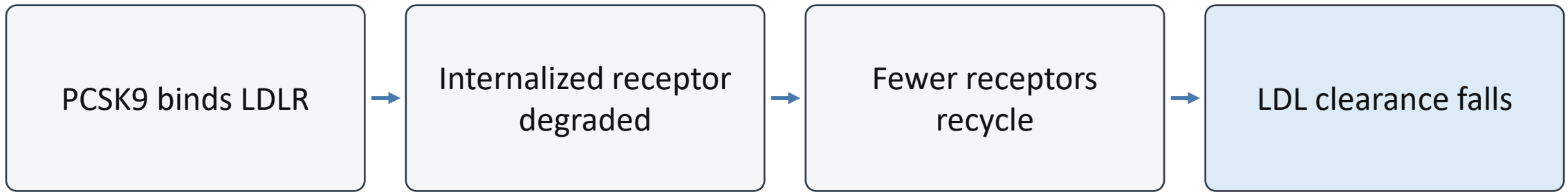
- The textbook attributes approximately 80%–85% of familial hypercholesterolemia to LDLR mutations.
- The receptor defect interferes directly with hepatic uptake of circulating LDL.
- Loss of effective LDL receptors also compromises hepatic uptake of IDL.
- More than 2,000 LDLR mutations are described in the supplied section.

ApoB defects: The ligand is abnormal



The receptor may be present, but its ligand cannot engage it efficiently.

PCSK9 gain of function: Receptor loss



Textbook estimate: Activating PCSK9 variants account for approximately 1%–2% of FH.

Approximate gene contributions in the source

Defect	Approximate FH cases	Primary mechanism
LDLR	80%–85%	Receptor quantity or function
APOB	5%–10%	Ligand–receptor binding
PCSK9	1%–2%	Enhanced receptor degradation

Heterozygous FH: Partial receptor capacity

Genotype

One disease-associated LDLR allele and one functional allele.

Functional effect

Approximately half the normal complement of high-affinity LDL receptors model.

Heterozygous FH: Biochemical expression

- The supplied source describes a two- to three-fold rise in plasma cholesterol from birth.
- Persistently elevated LDL promotes tendinous xanthomas in adult life.
- Premature atherosclerosis results from cumulative vascular exposure to cholesterol.
- The textbook estimates heterozygous LDLR-related FH at approximately 1 in 200 individuals.

Severe biallelic disease: A dose effect

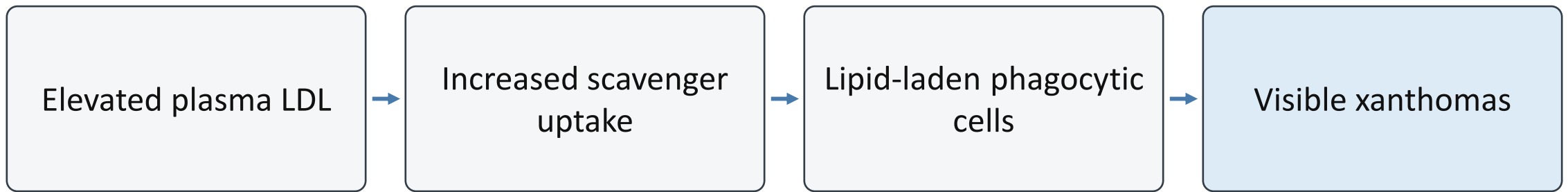
Receptor activity

Two severely affected alleles can leave little or no normally functioning LDL receptor activity.

Clinical burden

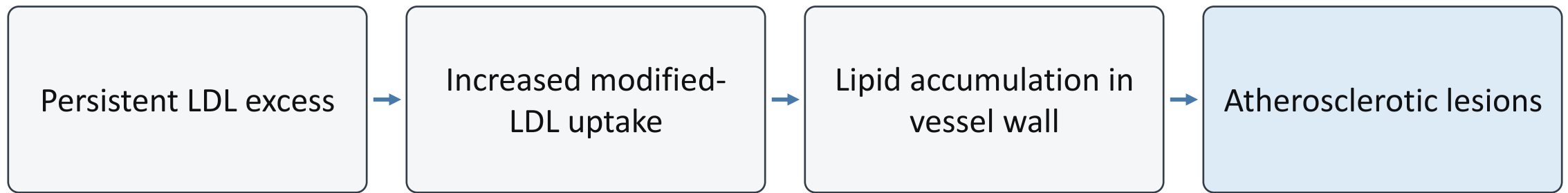
The source describes five- to six-fold plasma cholesterol elevation with early tissue and vascular lesions.

Xanthomas reveal excess cholesterol deposition



Tendinous xanthomas are emphasized in heterozygotes; Skin xanthomas may appear early in severe biallelic disease.

Premature atherosclerosis: Vascular consequence



The vascular mechanism links a receptor defect to coronary, cerebral, and peripheral disease.

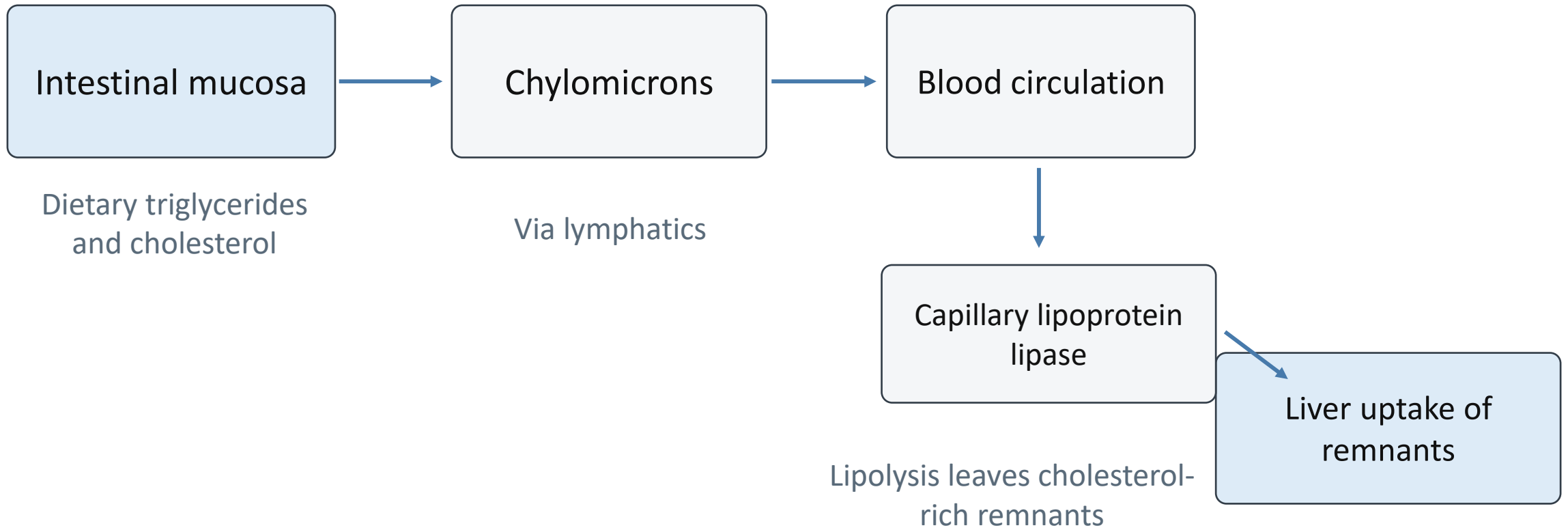
Severe disease may cause very early infarction

- Early coronary, cerebral, and peripheral atherosclerosis is described in severe biallelic FH.
- Myocardial infarction may occur before the age of 20 years in severely affected individuals.
- In the cited large-scale studies, FH was reported in 3%–6% of myocardial infarction survivors.
- These are observations, not newly verified 2026 prevalence estimates.

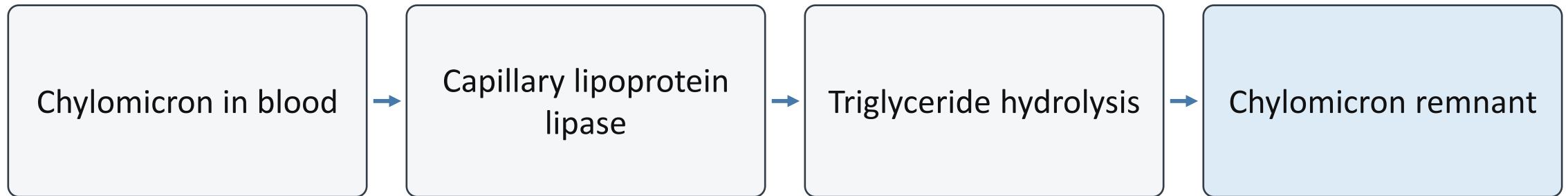
Disease severity follows residual pathway function

Feature	Heterozygous LDLR-FH	Severe biallelic LDLR-FH
LDL receptor capacity	Partially retained	Very limited or absent
Cholesterol change	Two- to three-fold	Five- to six-fold
Typical consequences	Adult xanthomas; Premature disease	Early xanthomas and vascular disease

Dietary cholesterol enters via chylomicrons



Lipoprotein lipase acts in peripheral capillaries



This lipolysis occurs in the capillaries of adipose tissue and muscle.

The liver is central to cholesterol traffic

Incoming

Chylomicron remnants bring dietary cholesterol from the circulation.

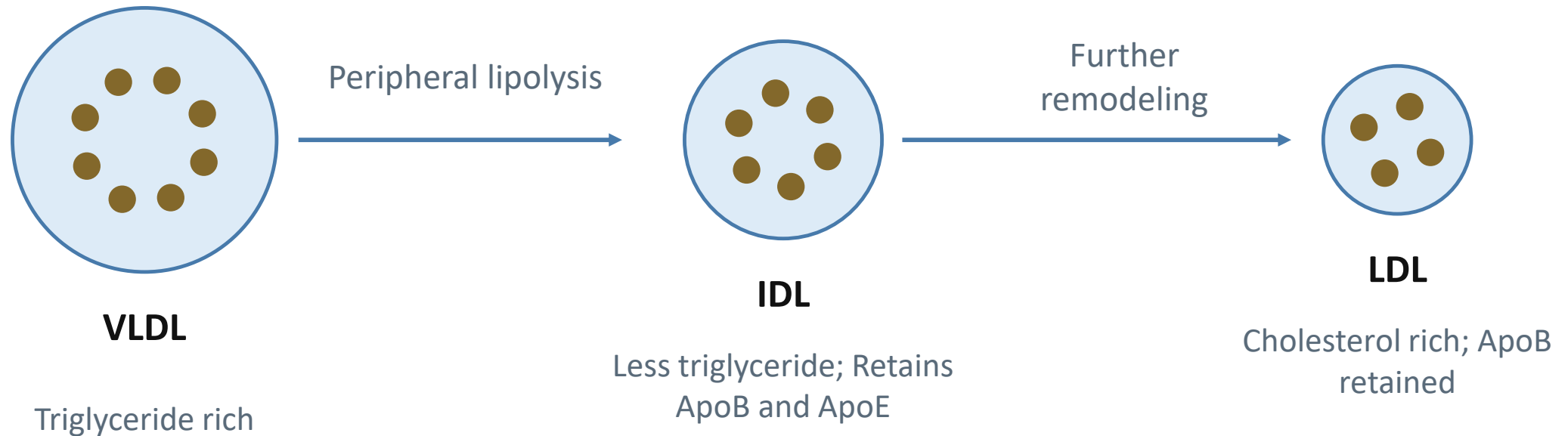
Production

The liver synthesizes cholesterol and secretes VLDL particles.

Disposal

Cholesterol can be secreted into bile as free cholesterol or bile acids.

VLDL begins the endogenous LDL pathway



VLDL contains several apolipoproteins

ApoB

Retained throughout VLDL
→ IDL → LDL processing.

ApoC

Present on VLDL; Lost during
conversion to IDL.

ApoE

Retained in IDL, where it
supports receptor
recognition; Later largely
removed.

VLDL lipolysis forms IDL

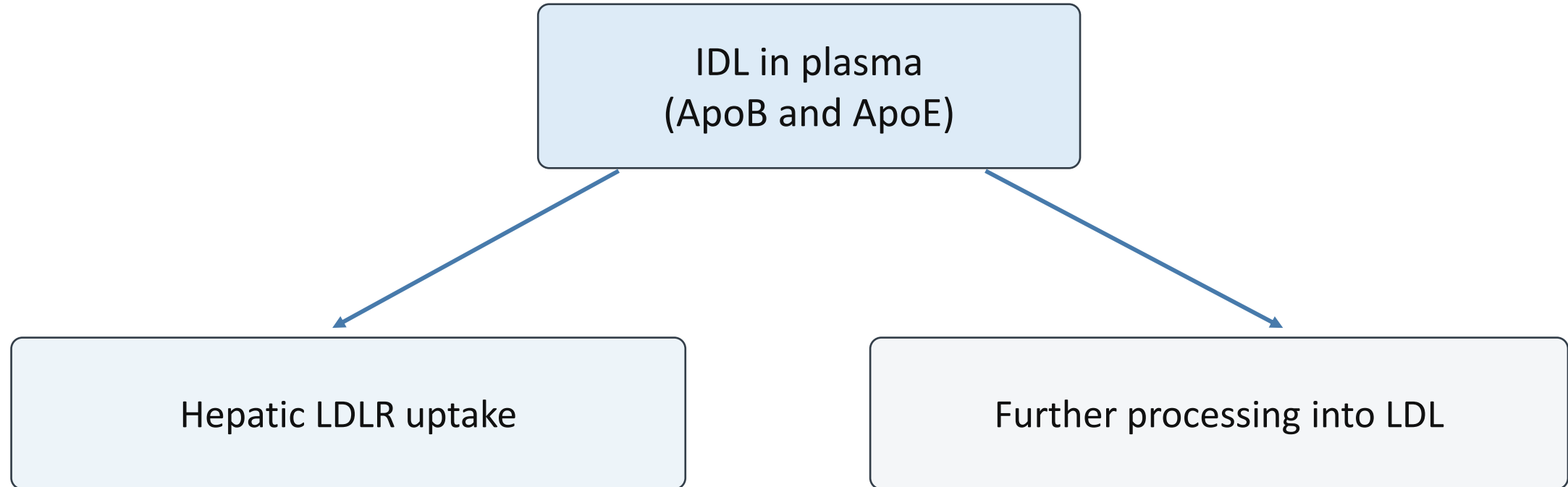
VLDL

Triglyceride-rich particles carry ApoB, ApoC, and ApoE.

IDL

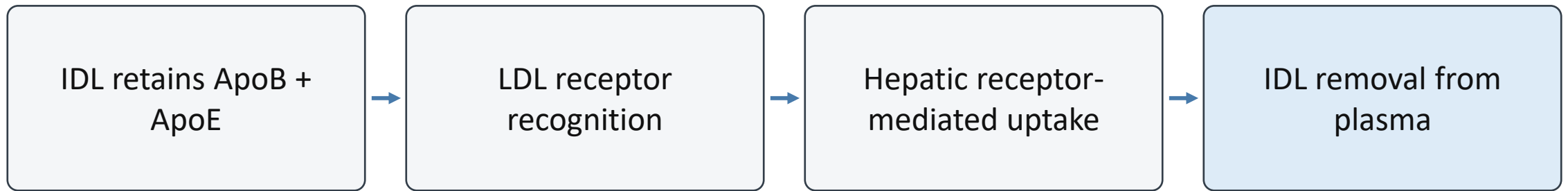
After lipolysis, the particles contain less triglyceride, more cholesteryl ester, and retain ApoB plus ApoE.

IDL has two alternative fates



Approximately 50% of newly formed IDL enters the rapid hepatic uptake pathway in the source.

LDLR recognizes ApoB and ApoE in IDL



The same receptor is therefore important for both IDL and LDL homeostasis.

LDL carries cholesterol and ApoB-100

Particle composition

IDL remodeling yields a cholesterol-rich LDL particle that retains ApoB-100.

Cell recognition

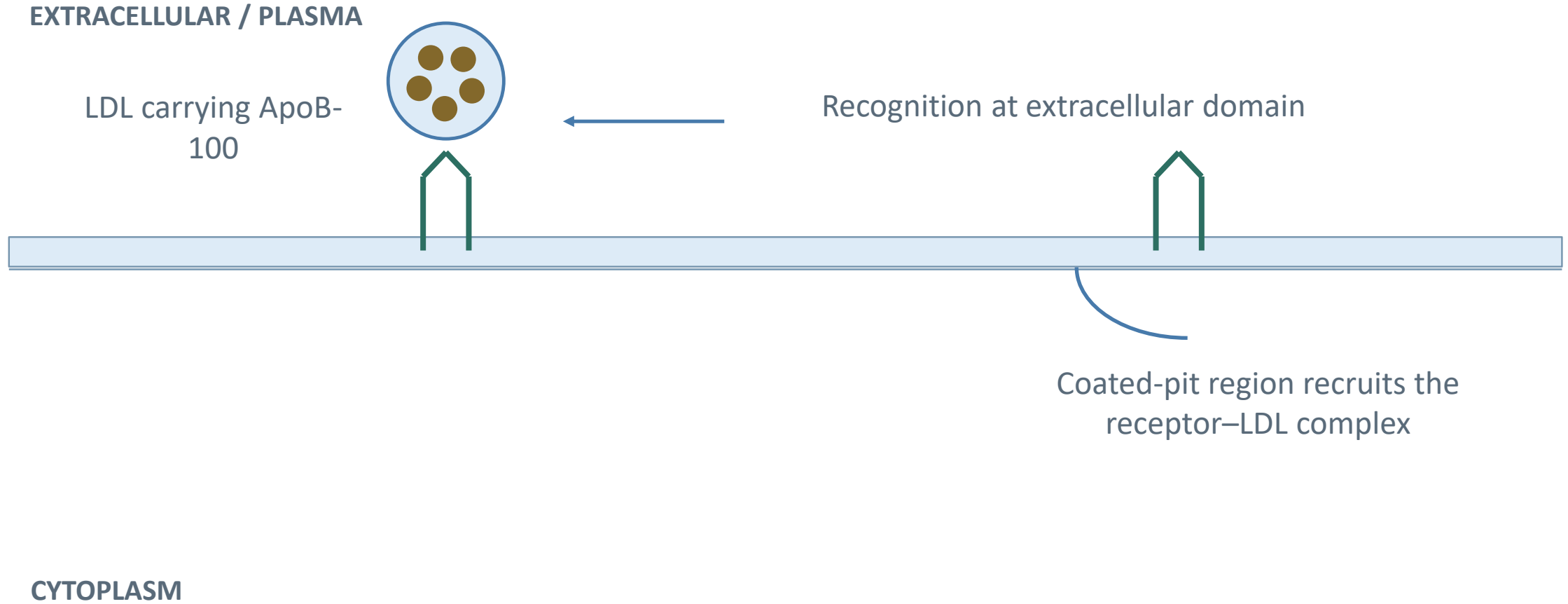
ApoB-100 serves as the ligand for high-affinity LDL receptors on susceptible cells.

Hepatic LDL clearance is quantitatively dominant

About 70% of plasma LDL is cleared by the liver

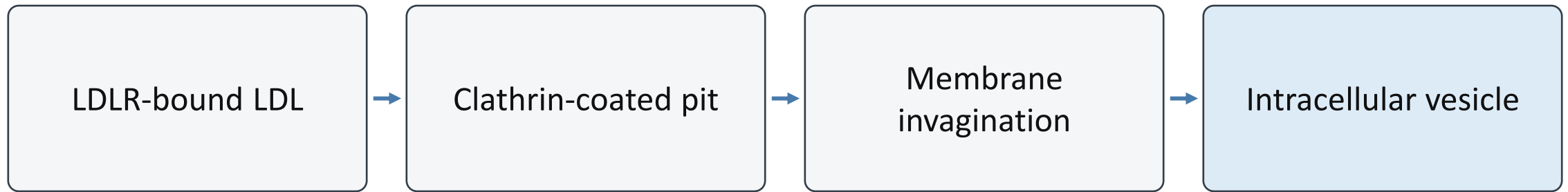
Other LDLR-expressing tissues include fibroblasts, lymphocytes, smooth muscle cells, and adrenocortical cells.

Surface binding occurs in coated-pit regions



Schematic — cell membrane and receptor are not drawn to molecular scale.

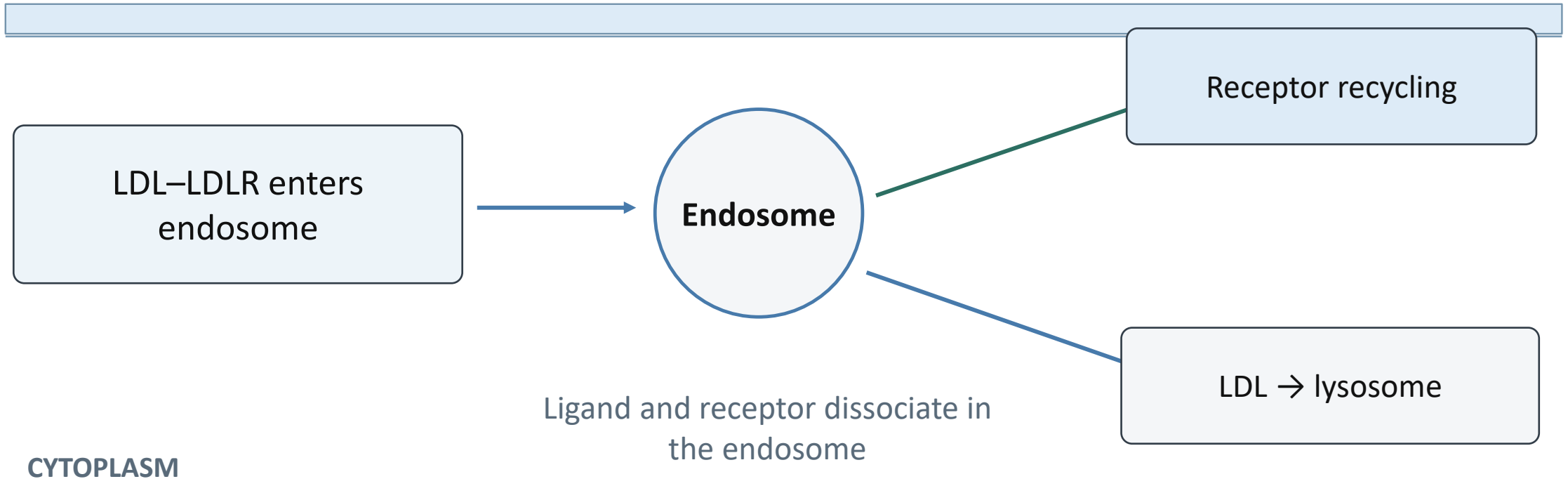
Clathrin-mediated uptake forms coated vesicles



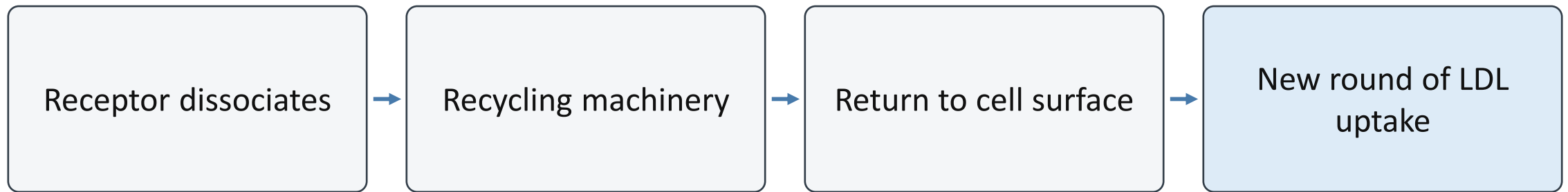
A defect in coated-pit clustering can stop uptake even when ligand binding is preserved.

Endosomal sorting separates ligand and receptor

EXTRACELLULAR / PLASMA

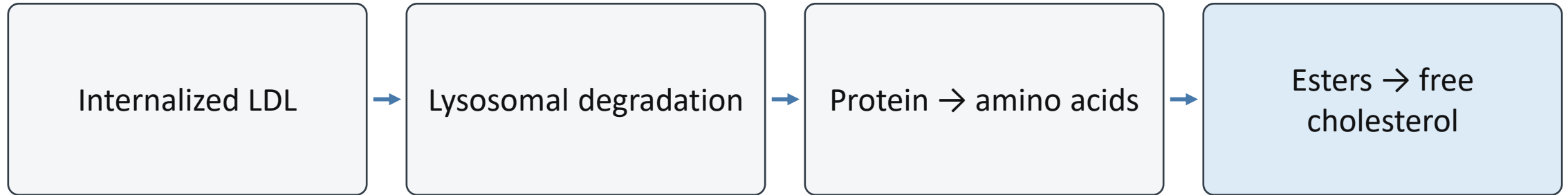


Receptor recycling sustains repeated clearance



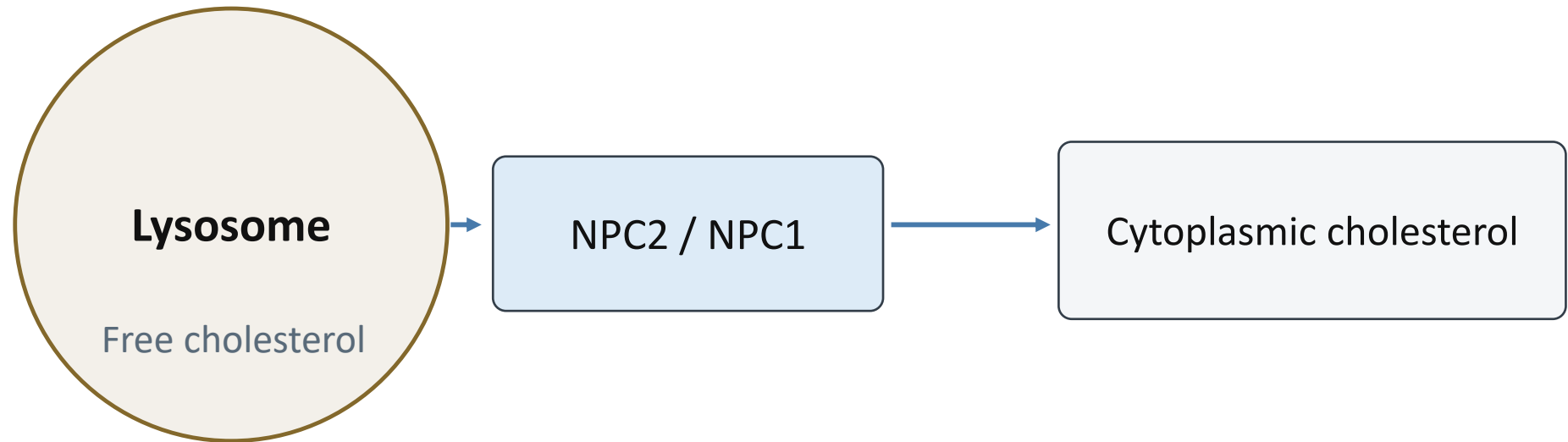
PCSK9 reduces receptor recycling by directing internalized receptors toward degradation.

Lysosomes release usable cholesterol



LDL apoproteins and cholesteryl esters undergo different lysosomal breakdown processes.

NPC1 and NPC2 allow lysosomal cholesterol exit



NPC1 and NPC2 are required for movement of free cholesterol out of lysosomes.

Intracellular cholesterol has two major roles

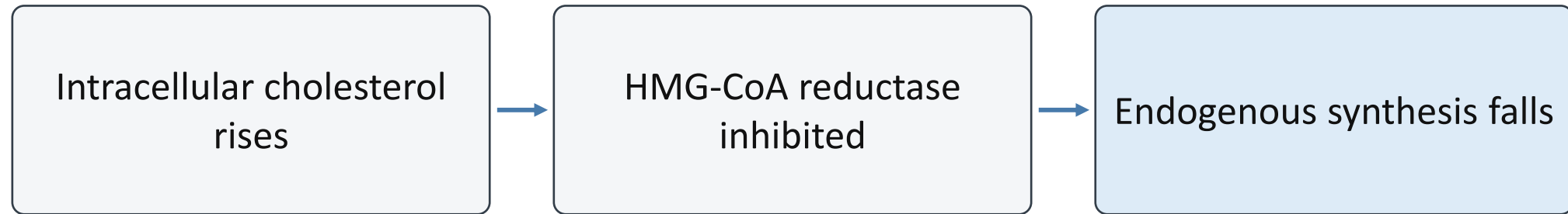
Cellular substrate

Supports synthesis and maintenance of cellular membranes.

Feedback regulator

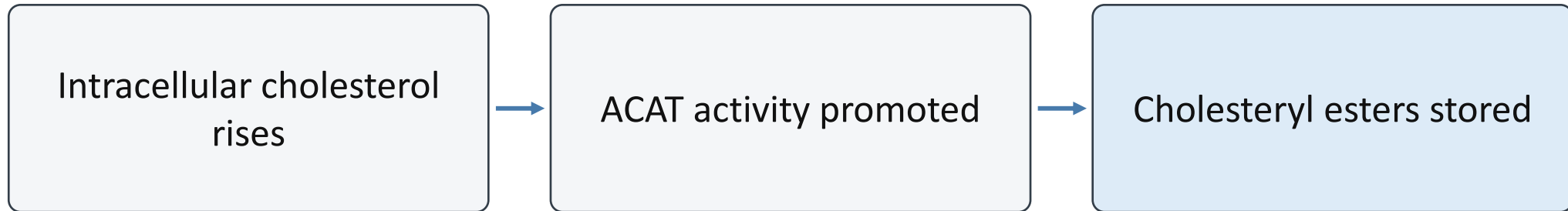
Adjusts cholesterol synthesis, cholesterol storage, and LDL receptor availability.

Cholesterol limits de novo synthesis



HMG-CoA reductase is the rate-limiting enzyme of cellular cholesterol synthesis.

Excess cholesterol is esterified for storage



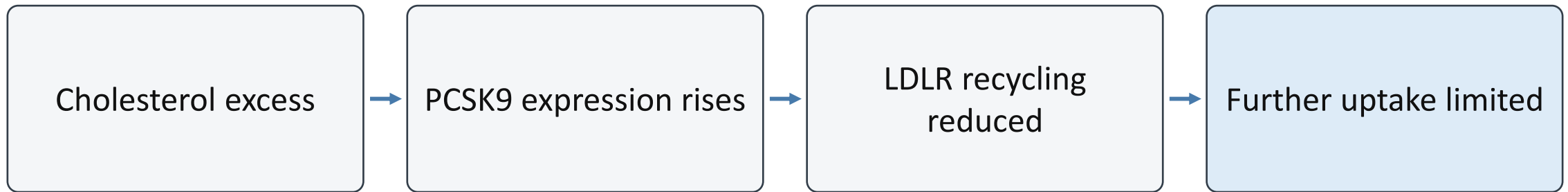
ACAT: Acyl-coenzyme A:cholesterol acyltransferase.

Cholesterol reduces LDLR synthesis



Feedback downregulation helps protect cells from excessive cholesterol accumulation.

Cholesterol induces PCSK9-mediated receptor loss

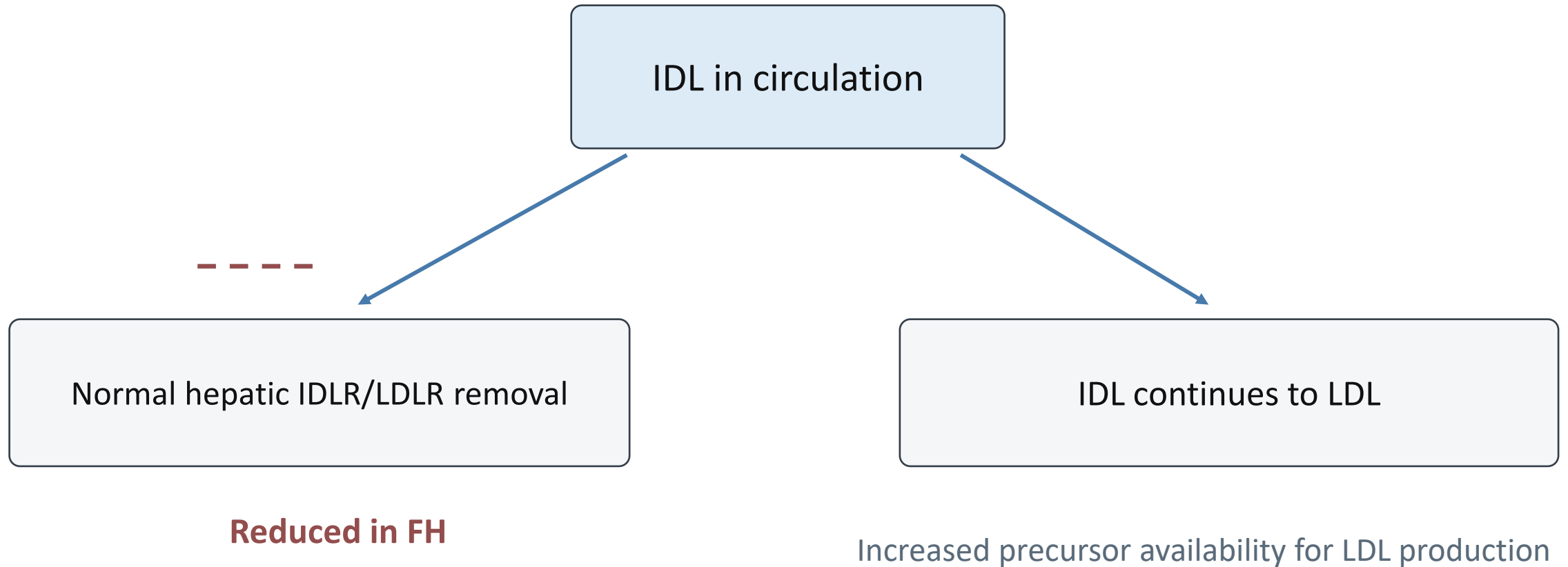


This as an additional feedback barrier to cholesterol overload.

Four coordinated responses to cholesterol excess

Regulated process	Response to intracellular cholesterol	Functional result
HMG-CoA reductase	Inhibition	Less de novo synthesis
ACAT	Activation	More ester storage
LDLR production	Suppression	Reduced receptor uptake
PCSK9 expression	Upregulation	Reduced LDLR recycling

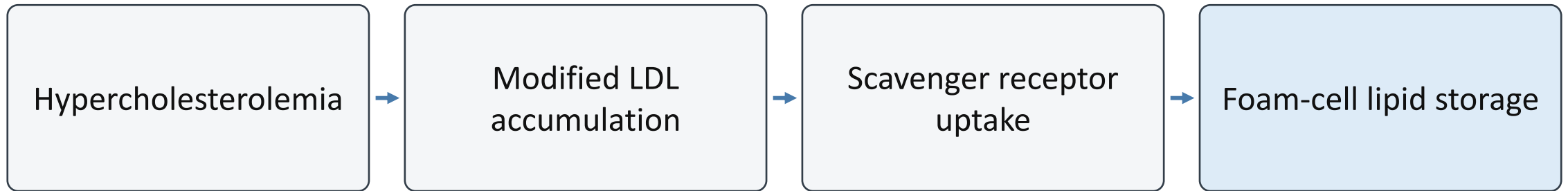
Reduced LDLR activity also diverts IDL into LDL



LDLR and scavenger pathways differ

Characteristic	LDL receptor pathway	Scavenger pathway
Principal particles	Native LDL; IDL	Chemically modified LDL
Dominant setting	Normal LDL clearance	Prominent with LDL excess
Relevant cells	Especially hepatocytes	Monocytes and macrophages
Disease link	FH clearance defect	Xanthomas and atherogenesis

Modified LDL uptake can overwhelm phagocytes

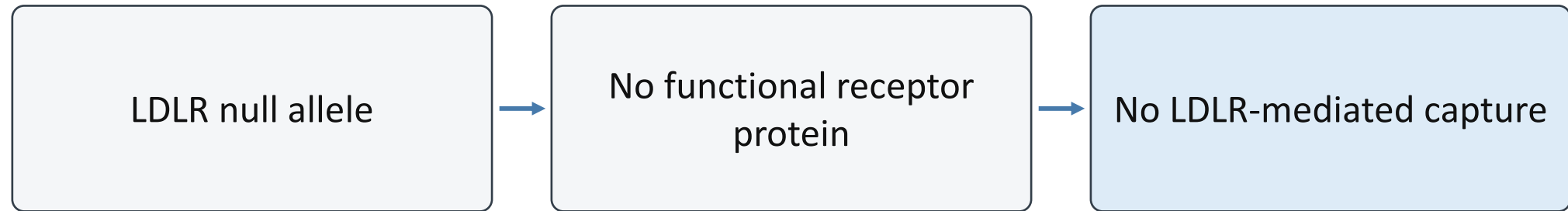


In the source, increased scavenger traffic explains xanthoma formation and contributes to atherosclerosis.

LDLR mutations fall into six functional classes

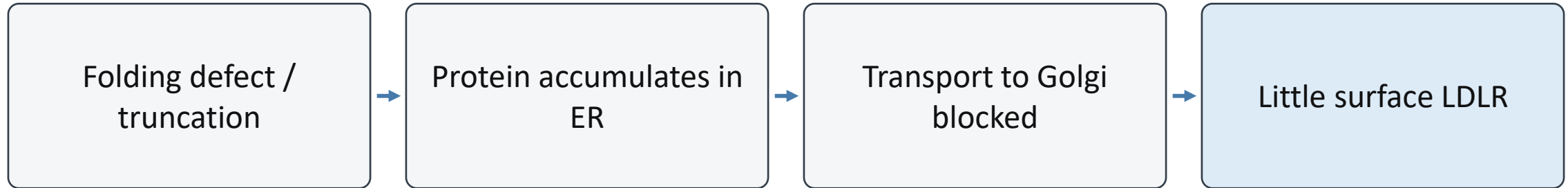
Class	Impaired function	Where the problem occurs
I	Receptor synthesis	Protein production
II	Receptor transport	ER → Golgi
III	Ligand binding	Cell surface
IV	Coated-pit clustering	Plasma membrane
V	Receptor recycling	Endosome
VI	Hepatocyte targeting	Basolateral membrane

Class I: Failure to synthesize LDLR



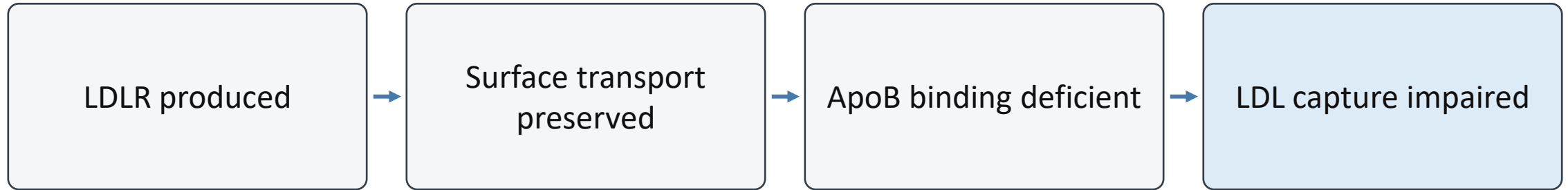
Class I as relatively uncommon.

Class II: Receptor retained in endoplasmic reticulum



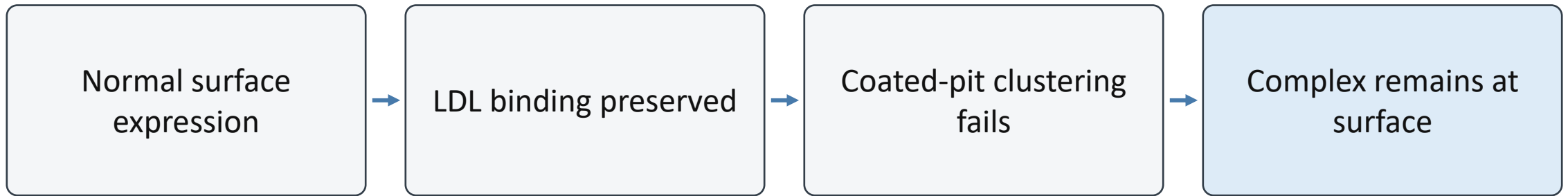
In contrast to class I, the receptor protein is synthesized but fails to traffic normally.

Class III: Defective ApoB binding



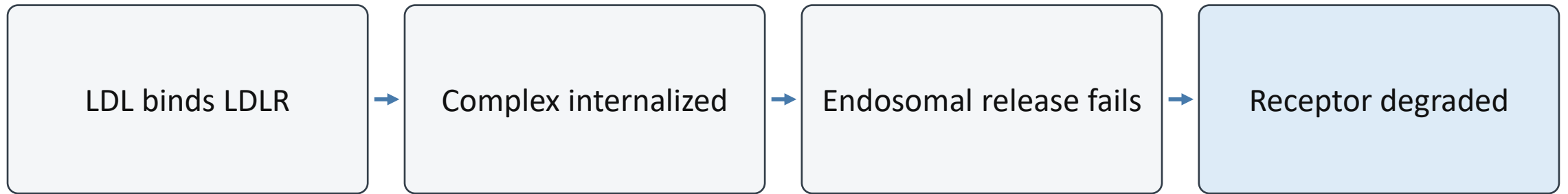
The LDLR reaches the plasma membrane but interacts poorly—or not at all—with LDL.

Class IV: Binding without internalization



An uptake defect can arise downstream of perfectly adequate ligand binding.

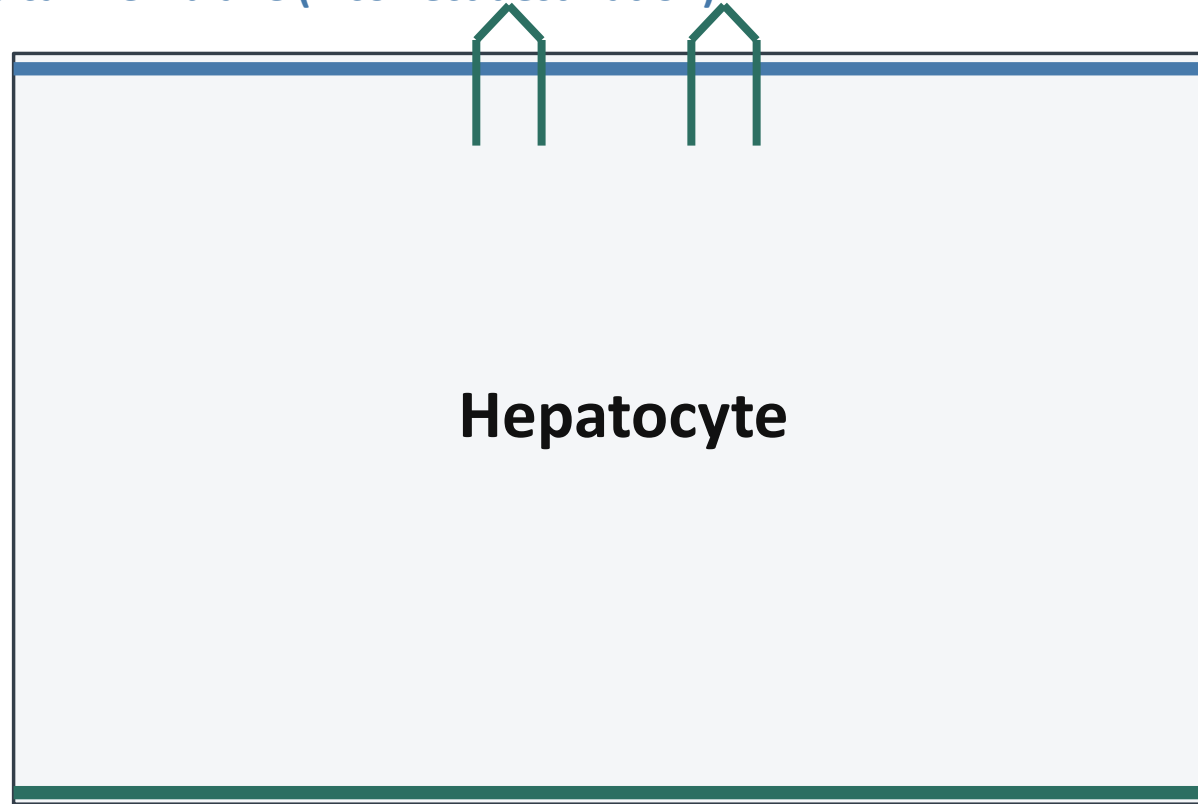
Class V: Dissociation and recycling fail



The required pH-dependent dissociation does not occur, trapping the receptor in the endosome.

Class VI: Hepatocyte membrane mistargeting

Apical membrane (incorrect destination)



Hepatocyte

Basolateral / sinusoidal membrane (required)

Mislocalization prevents efficient LDL clearance from plasma at the sinusoidal interface.

Classes I–III: The defect precedes uptake

Class	Present at cell surface?	Specific defect
I	No receptor synthesized	Protein production
II	Little or none	ER-to-Golgi transport
III	Yes	LDL binding

Classes IV–VI: Receptor location and reuse

Class	What remains intact?	What fails?
IV	Synthesis, transport, binding	Clustering / internalization
V	Synthesis, binding, endocytosis	Endosomal dissociation / recycling
VI	Synthesis of receptor protein	Basolateral membrane targeting

Similar LDL levels can arise through different defects

Receptor not available

Class I and class II mutations prevent effective receptor display.

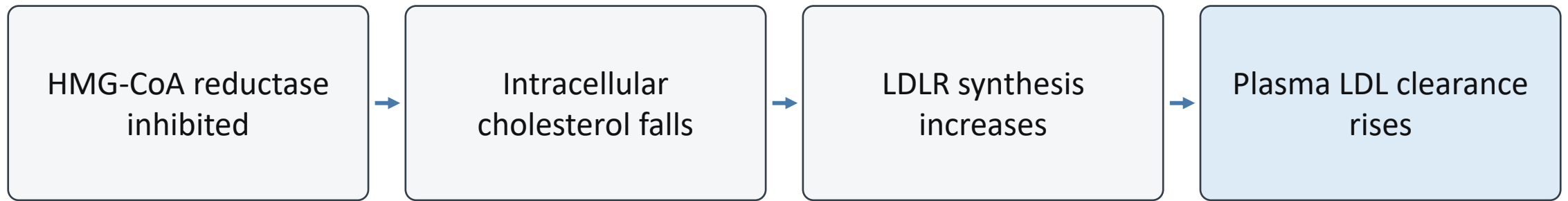
Receptor cannot perform

Class III and class IV impair binding or coated-pit uptake.

Receptor cannot return or localize

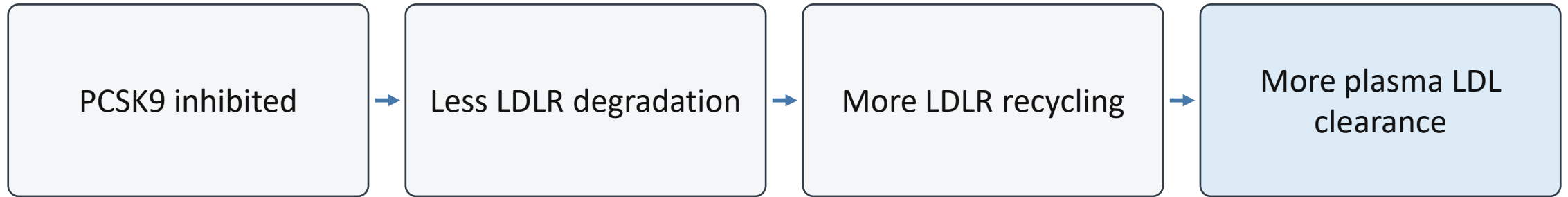
Class V impairs recycling; Class VI misdirects hepatocyte membrane targeting.

Statins work through receptor upregulation



The response depends on the pathway's capacity to produce functional LDL receptors.

PCSK9 antibodies preserve receptor availability



The supplied textbook reports clinical benefit when statins alone provide insufficient LDL reduction.

PCSK9 loss-of-function validates the pathway

Human genetic observation

Individuals with very low serum cholesterol carrying loss-of-function PCSK9 variants.

Causal interpretation

Less PCSK9-mediated degradation allows greater LDL receptor availability at the cell surface.

Two interventions converge on surface LDLR

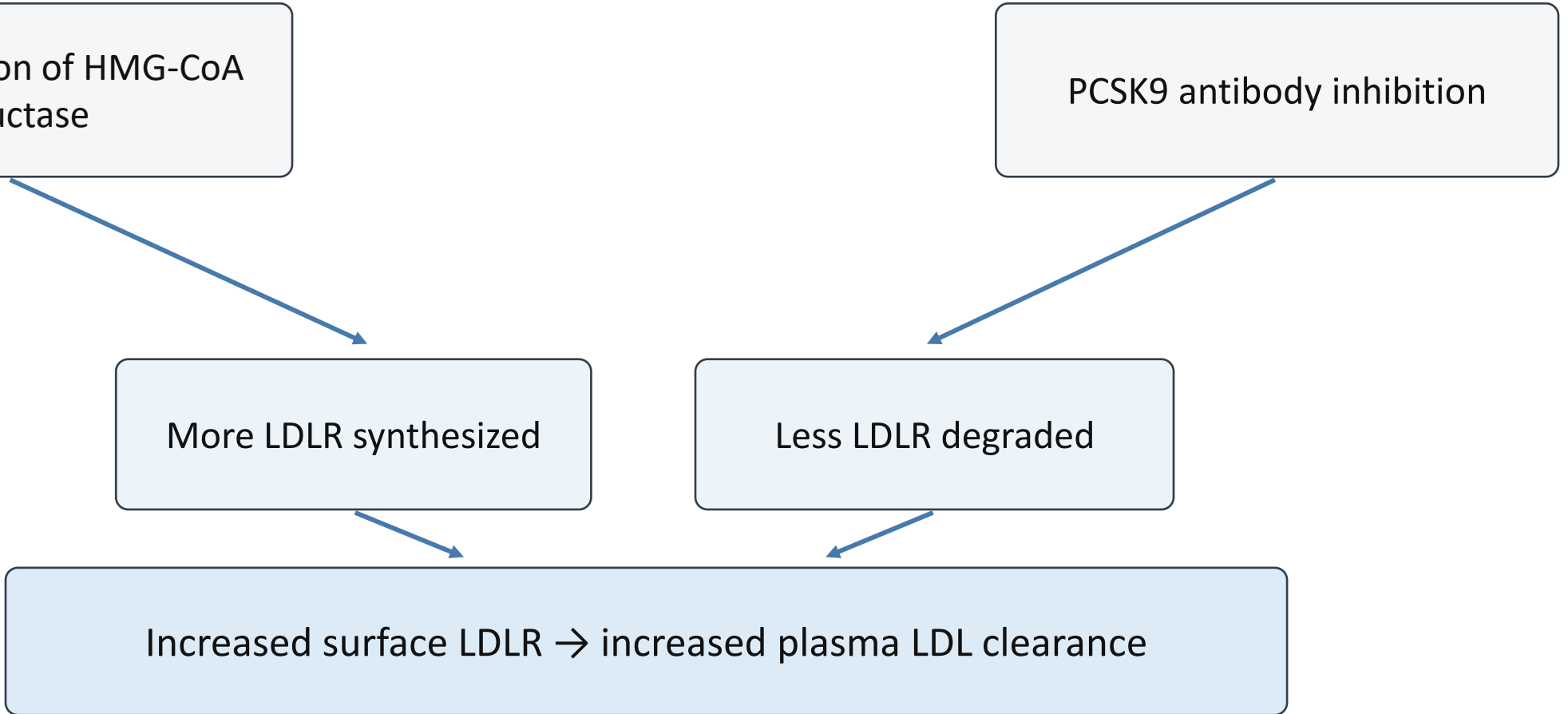
Statin inhibition of HMG-CoA reductase

PCSK9 antibody inhibition

More LDLR synthesized

Less LDLR degraded

Increased surface LDLR → increased plasma LDL clearance



Case: Tendon xanthomas and premature coronary disease

CLINICAL SCENARIO

An adult with lifelong marked hypercholesterolemia develops tendon xanthomas and premature atherosclerotic disease.

Which receptor-mediated pathway is most likely impaired?

Apply the LDLR → hepatic clearance → elevated LDL → tissue-deposition sequence.

Case: Severe childhood hypercholesterolemia

CLINICAL SCENARIO

A child develops skin xanthomas and early arterial disease with profoundly elevated circulating cholesterol.

Why does loss of receptor function on both alleles produce greater severity?

Compare residual LDLR activity in heterozygous versus severe biallelic disease.

Case: Normal LDL binding but failed endocytosis

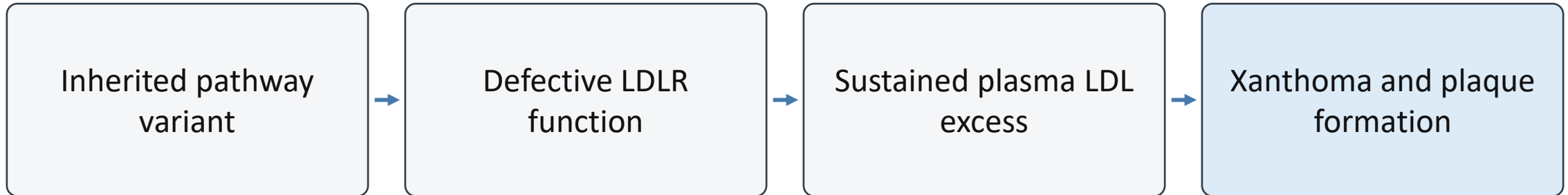
CLINICAL SCENARIO

A mutant LDL receptor is synthesized, reaches the cell surface, and binds LDL normally, but fails to enter coated pits.

Identify the LDLR mutation class and the affected process.

Class IV: Defective coated-pit clustering / internalization.

Integrated causal model of receptor-protein disease



LDLR, ApoB, and PCSK9 converge on the same physiological bottleneck: Hepatic LDL clearance.

Synthesis: Six classes are one mechanistic framework

- Synthesis, trafficking, binding, clustering, recycling, and membrane targeting are distinct receptor functions.
- A defect at any of these steps can reduce effective hepatic LDL clearance.
- An LDL receptor's presence at the cell surface does not guarantee a functioning uptake pathway.
- The same molecular map explains both the pathology and the rationale of receptor-directed treatment.

Concept check: test the mechanism, not the label

- Why can a class IV mutant receptor bind LDL but still fail to clear it?
- How does defective LDLR increase plasma LDL by two distinct mechanisms?
- Which familial hypercholesterolemia gene encodes the LDL receptor ligand?
- What cellular process explains cholesterol lowering by PCSK9 inhibition?