LIPOPROTEINS metabolism and pathophysiology

Marek Vecka

Function of lipids

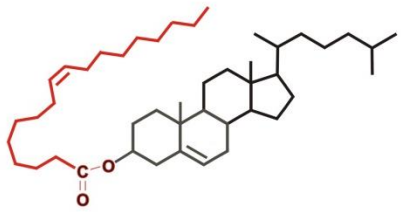
energy substrate
lipid microenvironment
insulation
membrane component
substrates for further metabolization
modifications of proteins/saccharides

Lipid transport

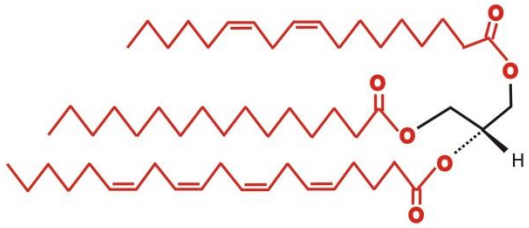
postprandial phase ***– digestion of lipids from the diet***

fasting state ***– delivery of lipids to the tissues in need***

Important lipid classes

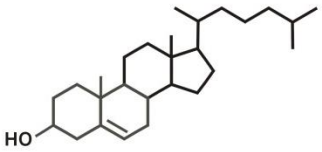


cholesteryl ester, CE

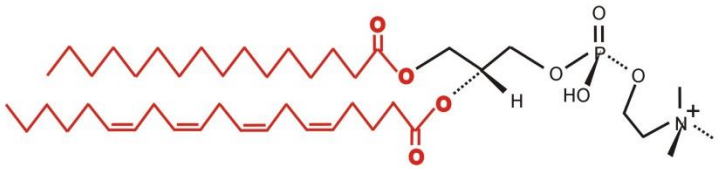


triacylglycerol, TAG (TG)

neutral = hydrophobic

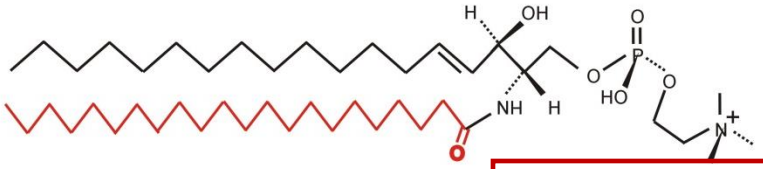


cholesterol, FC

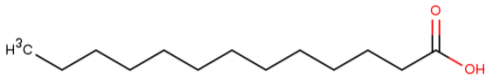


phosphatidylcholine, PC

polar = amphiphilic



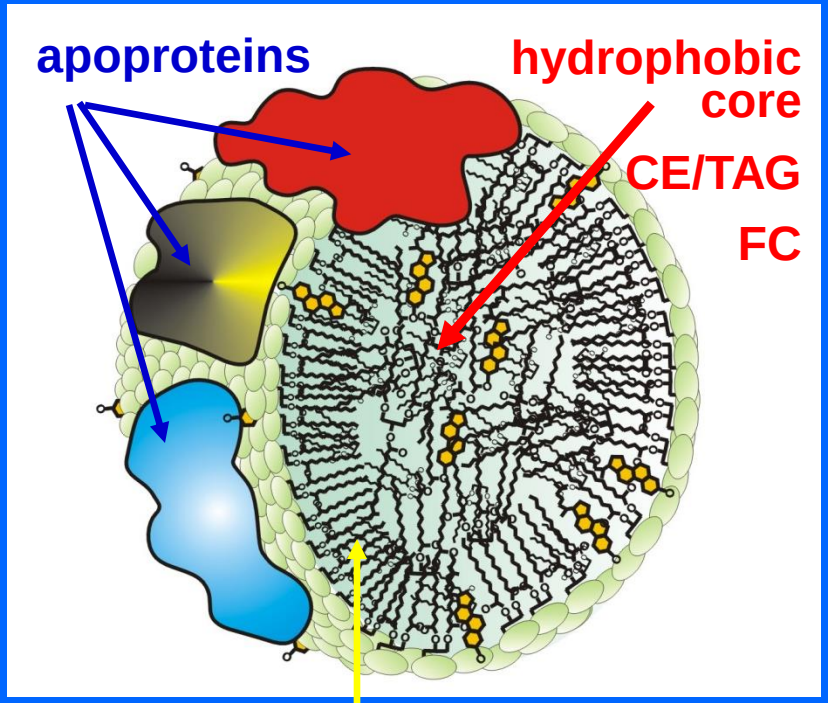
sphingomyeline,SPH



NEFA very polar

Structure of lipoprotein

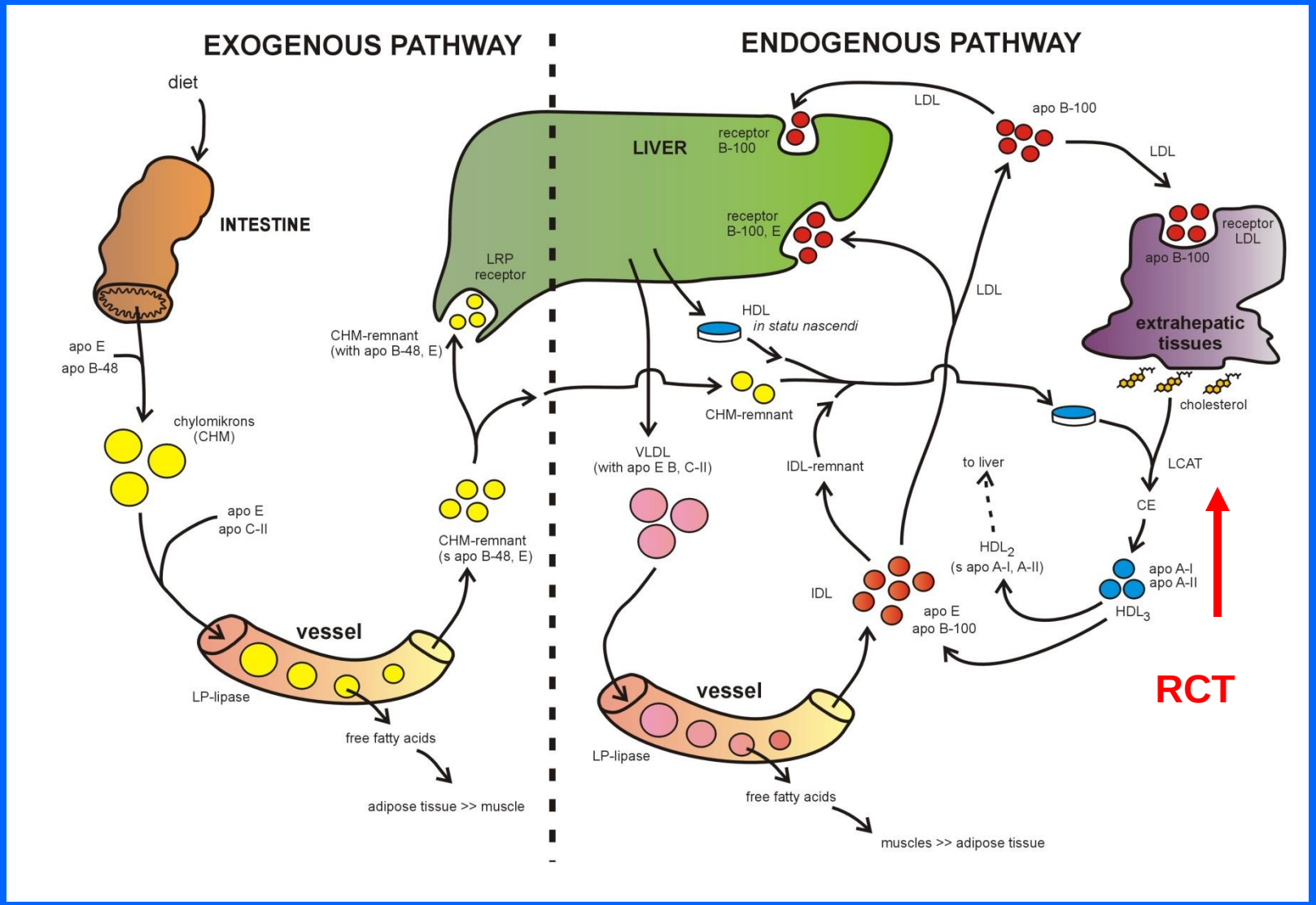
- cca spherical
- micellar
- noncovalent interaction between lipids and proteins
- lipid transporting system
- possible interchange of apoproteins, lipids between lipoproteins



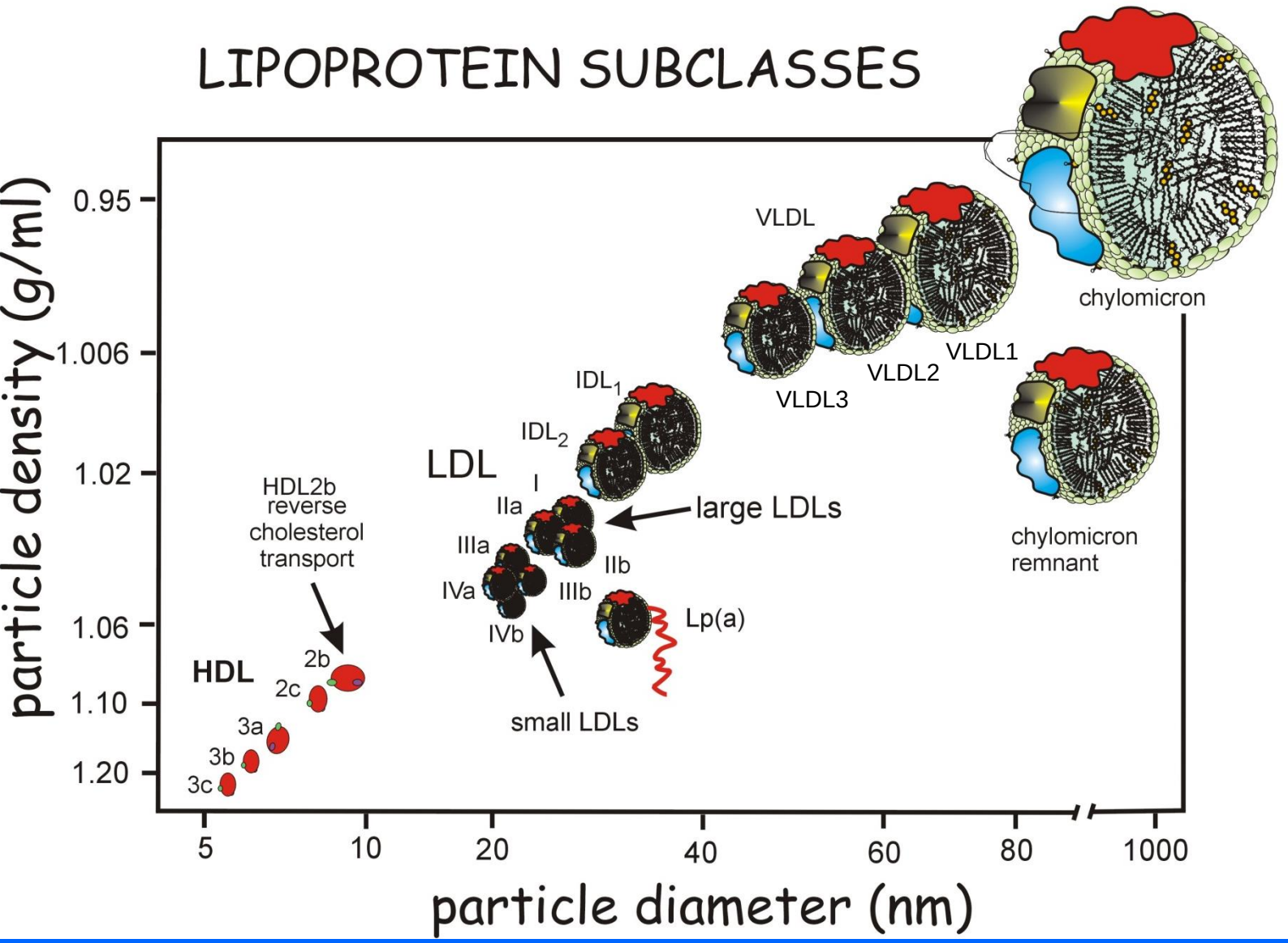
Plasma lipoproteins

Lipoprotein class	Major Lipid class	Apolipoproteins	Source
CM (chylomicrons)	TAG	A-I, A-II, A-IV, C-II, -III, B-48, E	intestine
remnant CM	TAG, CE	B-48, E	catabolism of CM
VLDL (very low density Lp)	TAG	B-100, C-II,-III, E	liver (intestine)
IDL (intermediate density Lp)	CE	B-100, C-II,-III, E	catabolism of VLDL
LDL (low density Lp)	CE	B-100	catabolism of IDL
HDL_2 (high density Lp) *subclass 2*	CE, PL	A-I, A-II	liver, intestine catabolism of CM and VLDL
HDL_3 (high density Lp) *subclass 3*	CE	A-I, A-II, minor apolipoproteins	HDL_2
lipoprotein [a]	CE	B-100 & apo [a]	liver

Metabolic lipoprotein pathway



Lipoprotein size



Plasma apolipoproteins

apolipoprotein = protein part of lipoprotein particle

many functions (intracellular ≠ extracellular)

Non-exchangeable apolipoproteins

structural function: apo B-48, apo B-100

receptor ligands: apo B-48, apo B-100

Exchangeable apolipoproteins

receptor ligands: apo E, apo A-I

structural function: apo A-I

modulation of enzyme activity: apo A-I, apo A-II, apo C-I, apo C-II, apo C-III

enzyme activity: apo K (PON)

acute phase reactant: apo I (SAA)

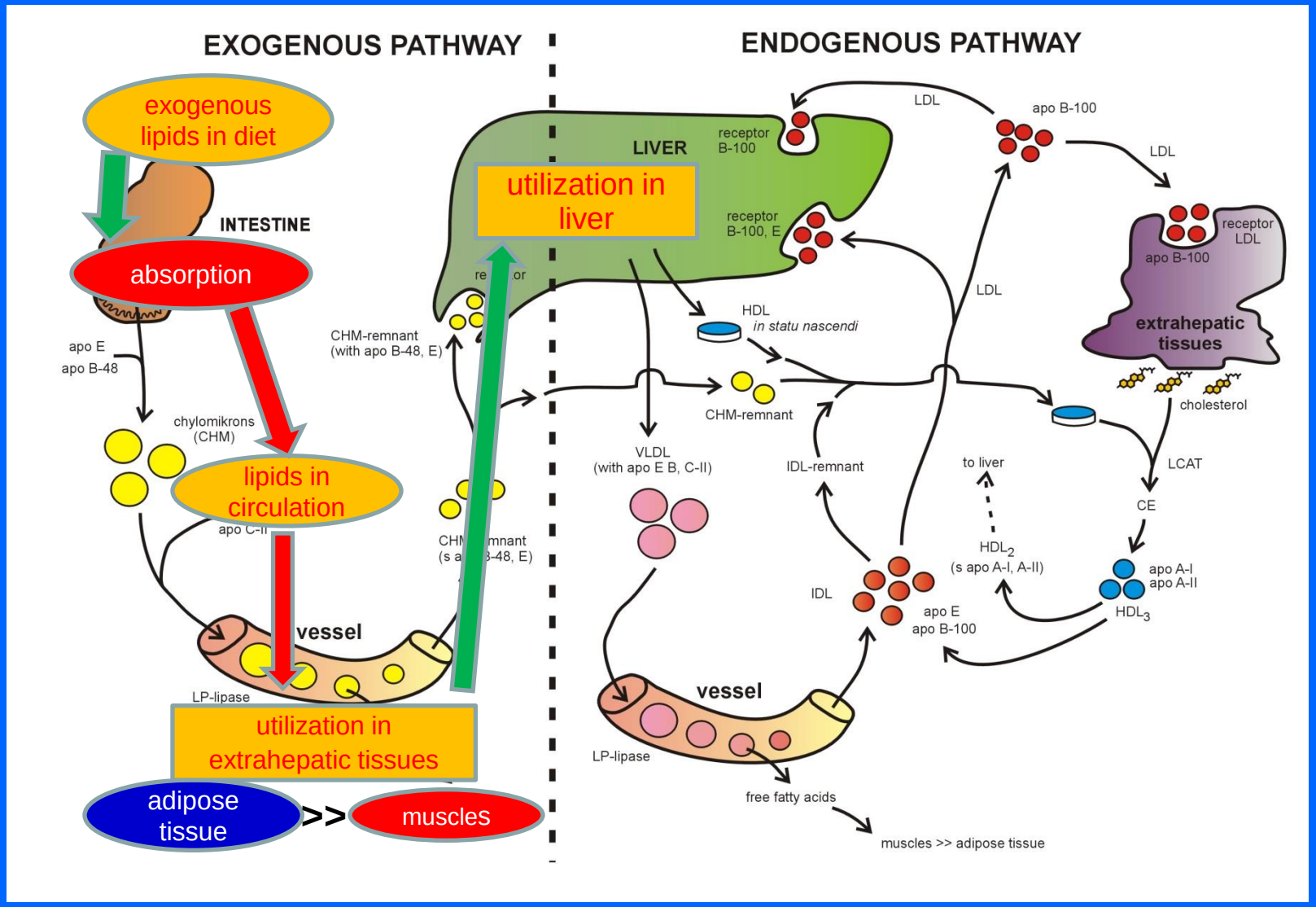
inhibition of metabolic cascades: apo (a) (thrombolysis?) apo J (inhibitor of terminal complement complex)

Important plasma apolipoproteins

apolipoprotein	major LP class	concentration (g/l)	function
A-I	$HDL_{2,3}$	1.20 - 1.40	LCAT activation HDL-receptor ligand, transport (HDL)
A-II	HDL_3	0.35 - 0.50	activation of hepatic lipase, transport (HDL)
A-IV	CM, $HDL_{2,3}$	< 0.05	RCT, absorption of exogenous TAG
B-100	VLDL, IDL, LDL	0.60 - 1.20	transport (VLDL, IDL, LDL), LDL-receptor ligand
B-48	CM, β-VLDL	< 0.05	absorption of lipids, apoB-48 receptor ligand transport (CM, remnant CM)
C-I	CM, VLDL	0.05 - 0.08	inhibition of CETP, LCAT activation
C-II	CM, VLDL	0.03 – 0.07	activation of LPL
C-III $_{0-3}$	CM, VLDL	0.10 - 0.12	catabolism of CM_R, inhibition of LPL
D	HDL_3	0.08 - 0.10	free cholesterol esterification?
E	CM, VLDL, HDL-E	0.03 - 0.05	LDL-receptor ligand, VLDL-receptor ligand, RCT LRP-receptor ligand, apoER2-receptor ligand

RCT - reverse cholesterol transport, LCAT - lecithin:cholesterol acyltransferase, LPL - lipoprotein lipase, CE - cholesterylester, TAG - triacyglycerol, CM_R - remnant CM, β-VLDL – remnant VLDL staying in plasma

Metabolic lipoprotein pathway



Lipid digestion

gastro-salivary phase

Lingual lipase (pH optimum 3.5-6)

secreted by von Ebner´s glands, acts also in stomach

TAG → 1,2-DAG, 2,3-DAG + FFA

Gastric lipase (pH optimum 3.5-5.4)

TAG → DAG + FFA/glycerol + FFA

significant contribution

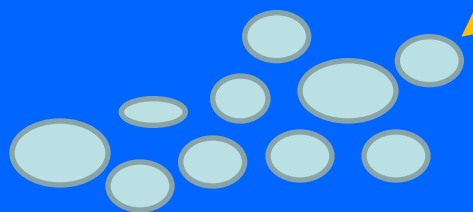
to the digestion (10-30 % of TAG)

gastric movements

peristaltic movements

grinding of the antrum

1. emulsification of lipids



Lipid digestion

intestinal phase - pancreatic lipases

Pancreatic lipase (pH optimum 6.5-9)

at the interface of lipid droplets

(facilitated by BA micellarization of products)

TAG → 2-MAG + FFA

Colipase

exposes the active site of pancreatic lipase

Pancreatic phospholipases PLA_1, PLA_2

activated by trypsin

PL → 2-lysoPL, 1-lysoPL + FFA

Cholesteryl ester hydrolase (BA activated lipase)

CE → FC + FFA

other substrates: retinyl esters, TAG, PL, Cer

2. lipolysis of lipids

Lipid digestion

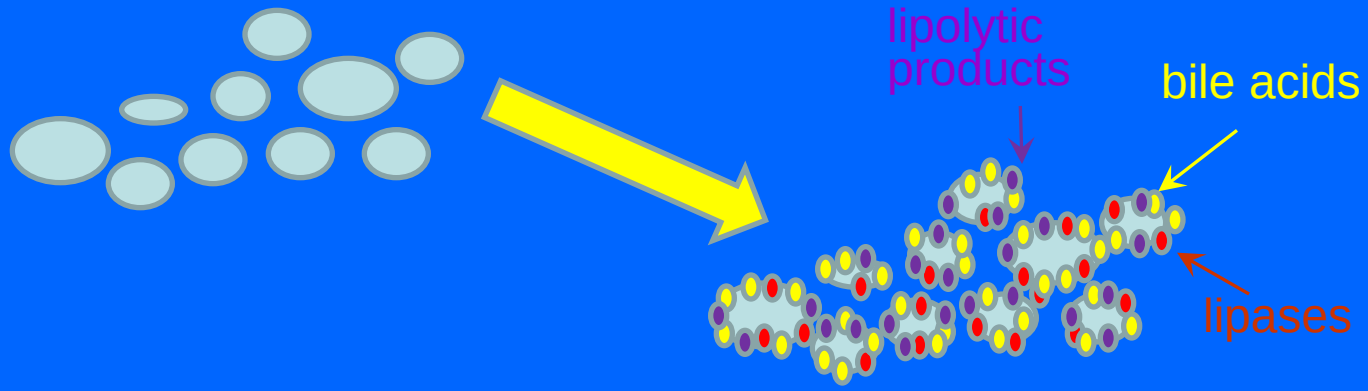
intestinal phase - pancreatic lipases

alkaline sphingomyelinase

SPH → Cer + P-choline

neutral ceramidase

Cer → sphingosine + FFA

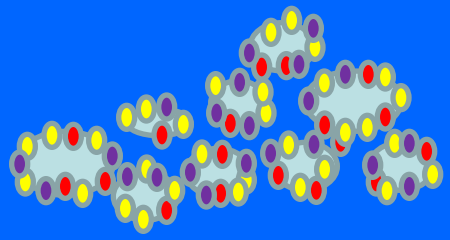


2. lipolysis of lipids

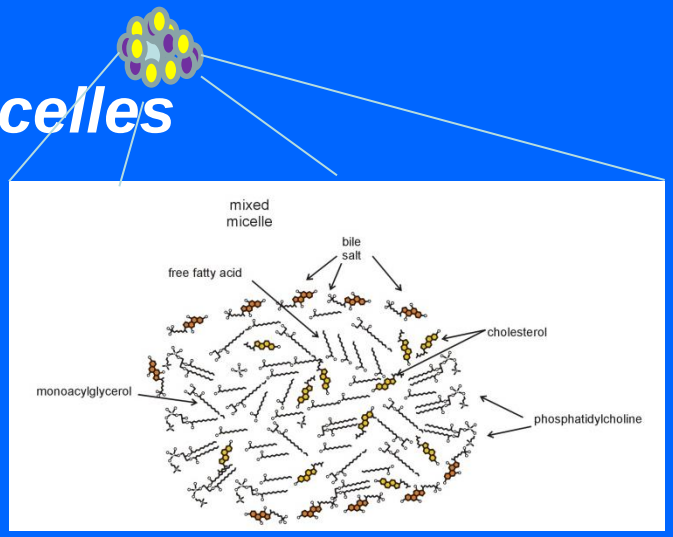
Lipid digestion

intestinal phase - formation of micelles

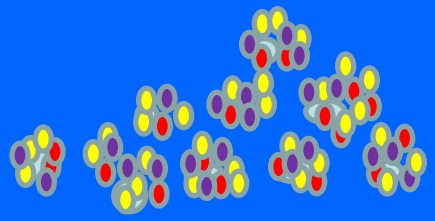
BA and PL displace lipolysis products from the water-oil interface



mixed micelles



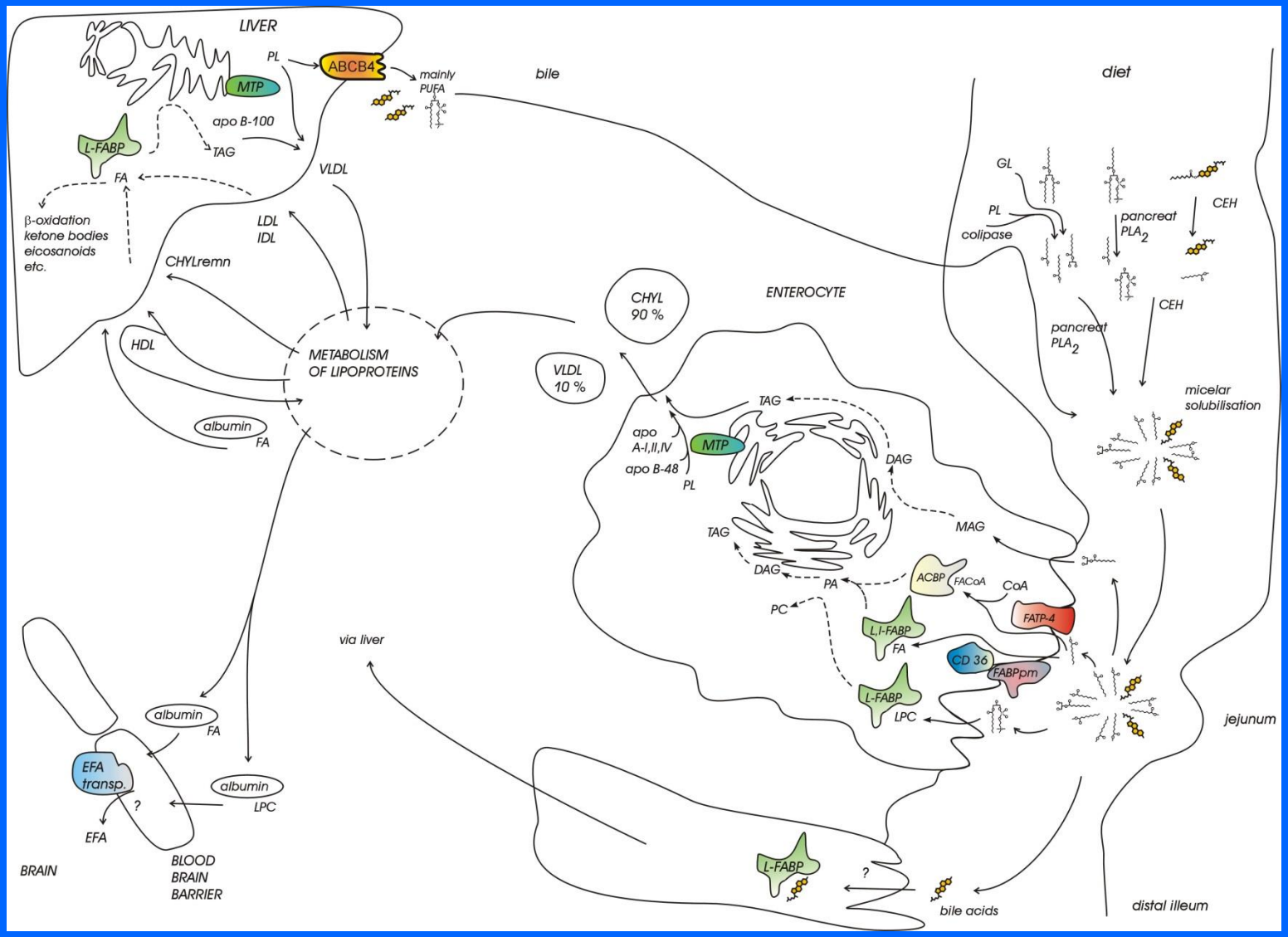
further lipolysis by lipases



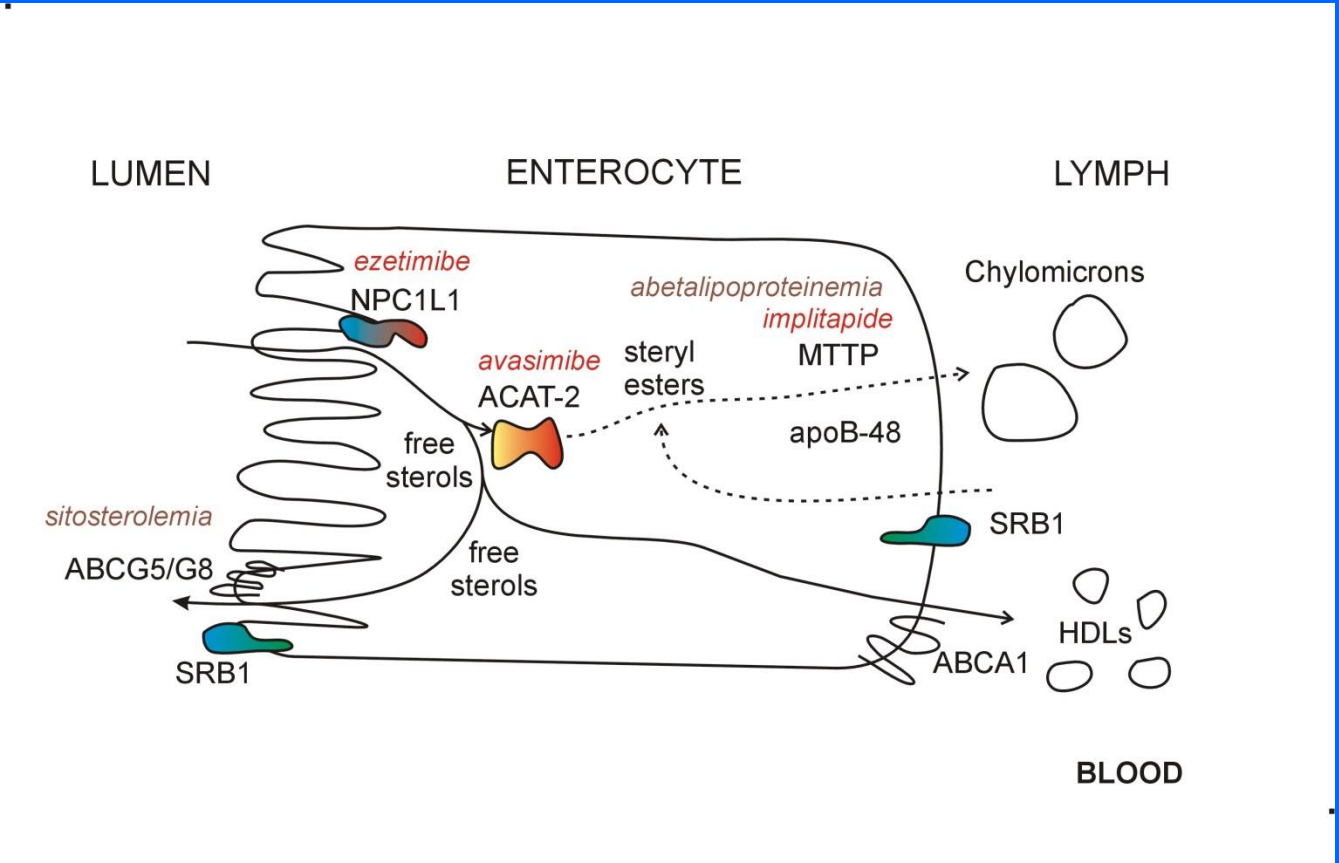
<u>3. solubilization of lipids</u>

4+5. translocation and intracellular metabolism of lipids

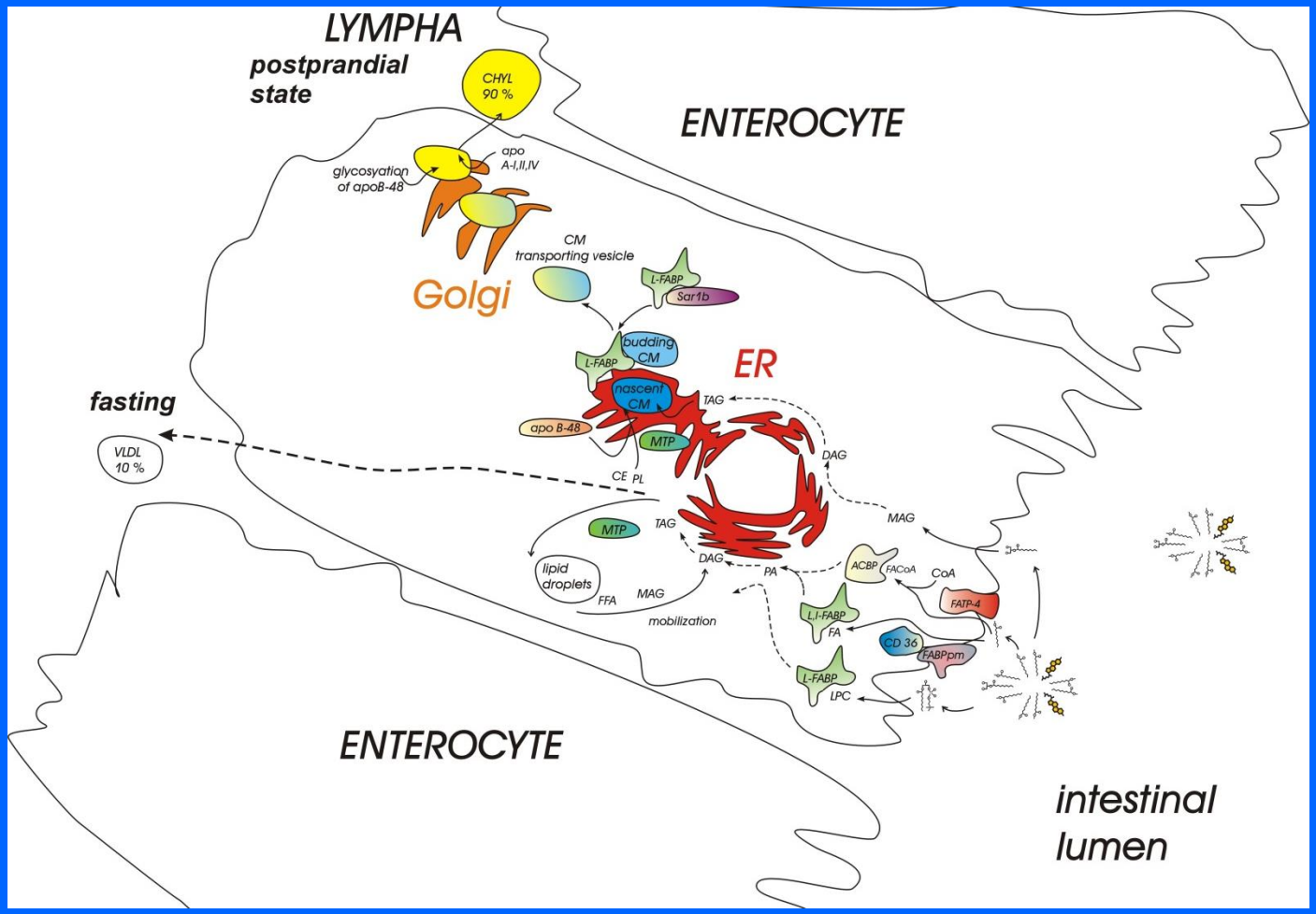
Lipid absorption – fatty acids



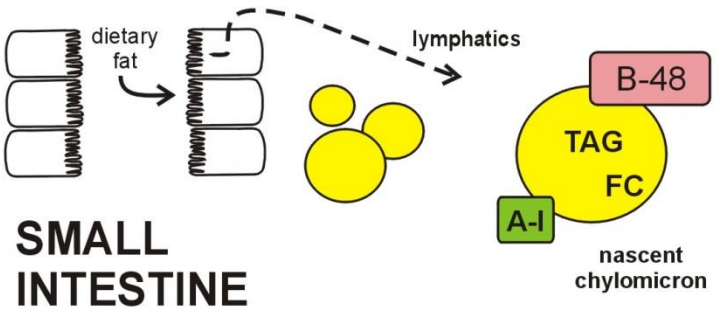
Lipid absorption – sterols



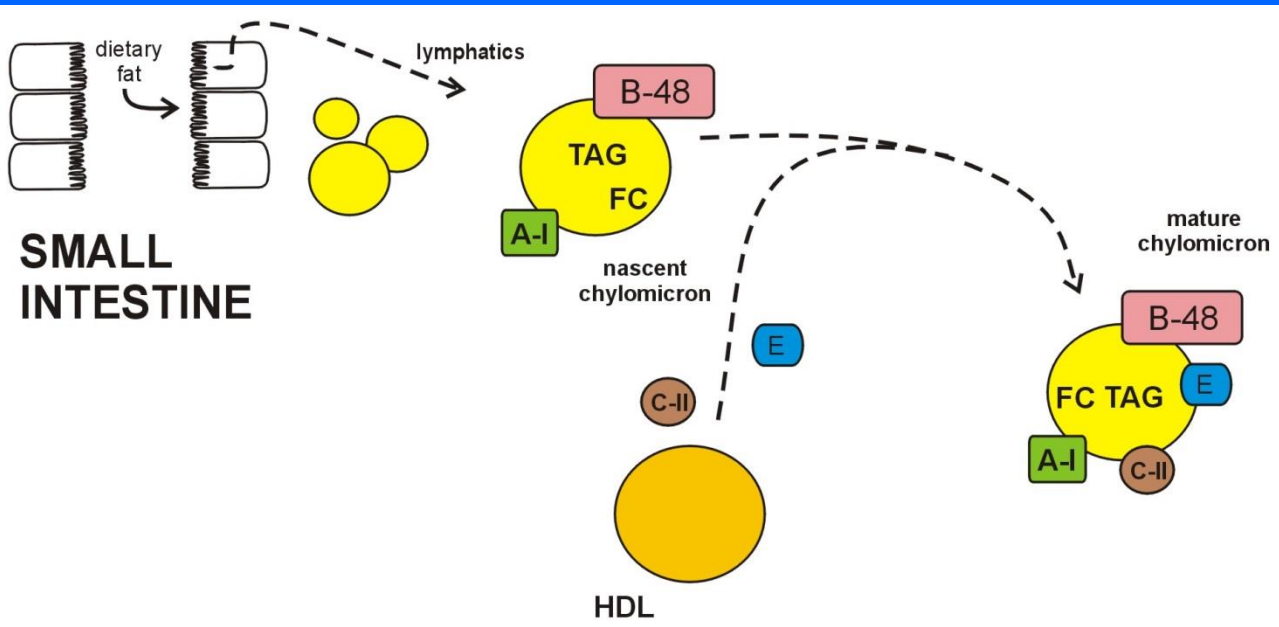
Assembly of chylomicrons



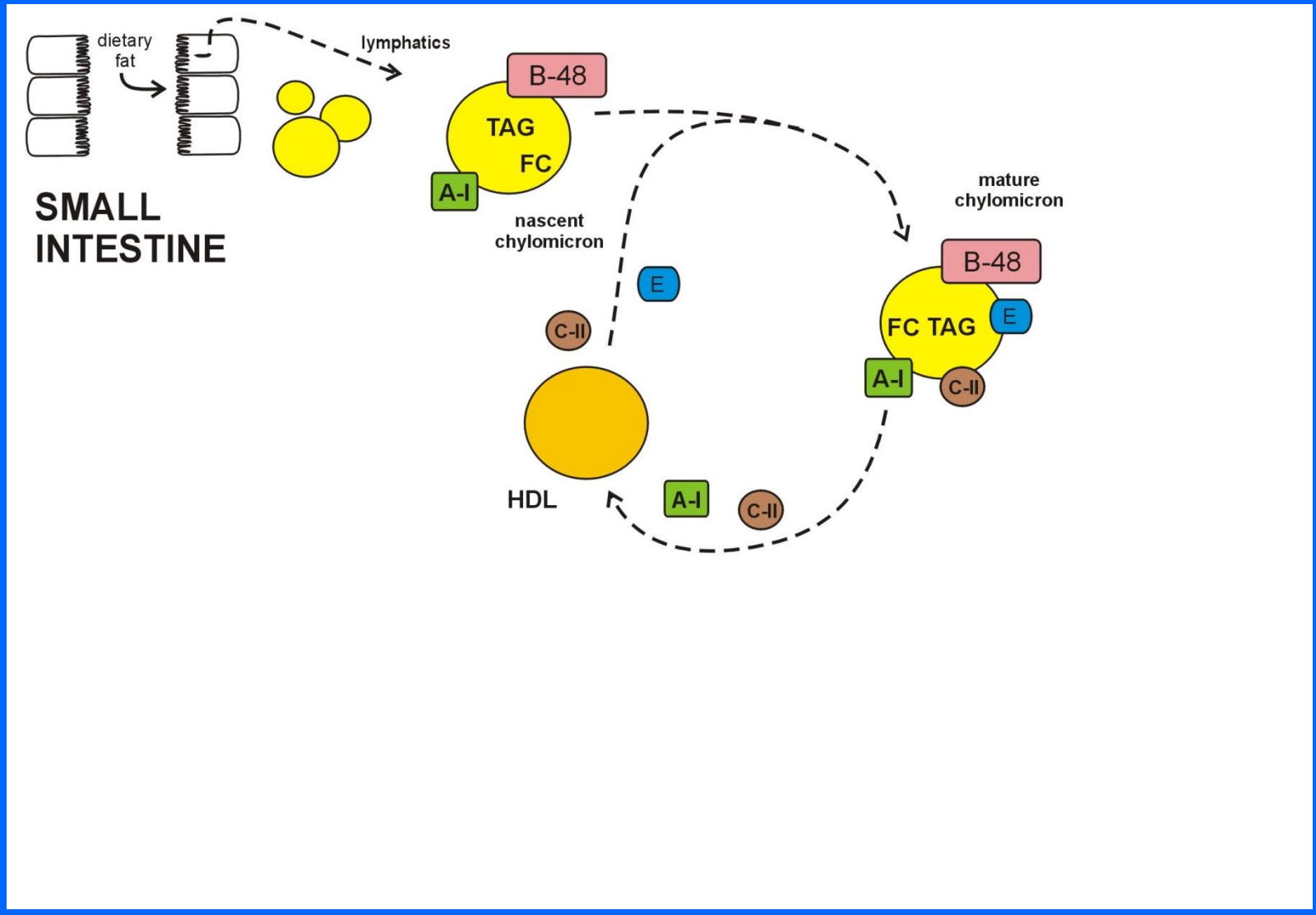
Chylomicrons



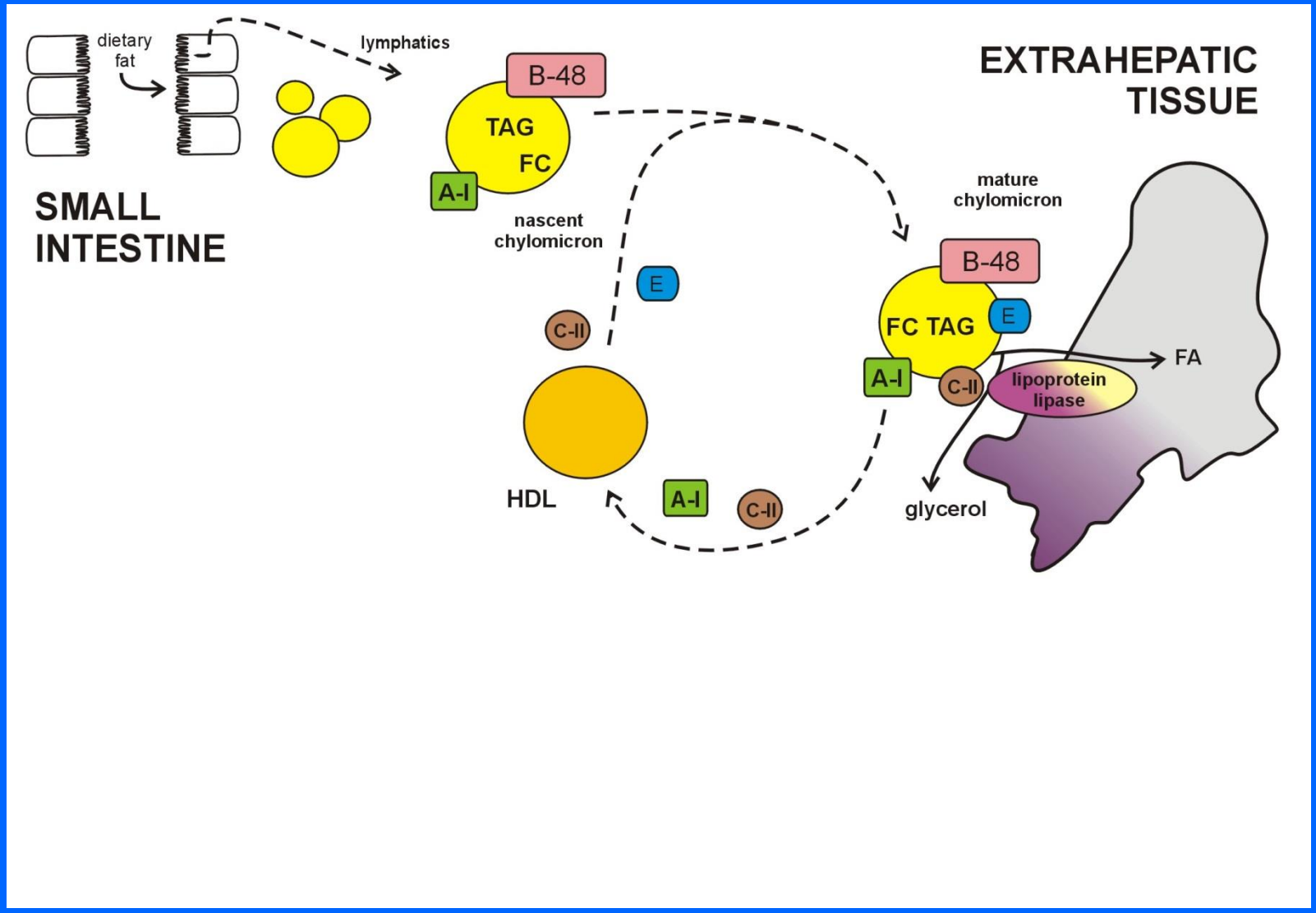
Chylomicrons



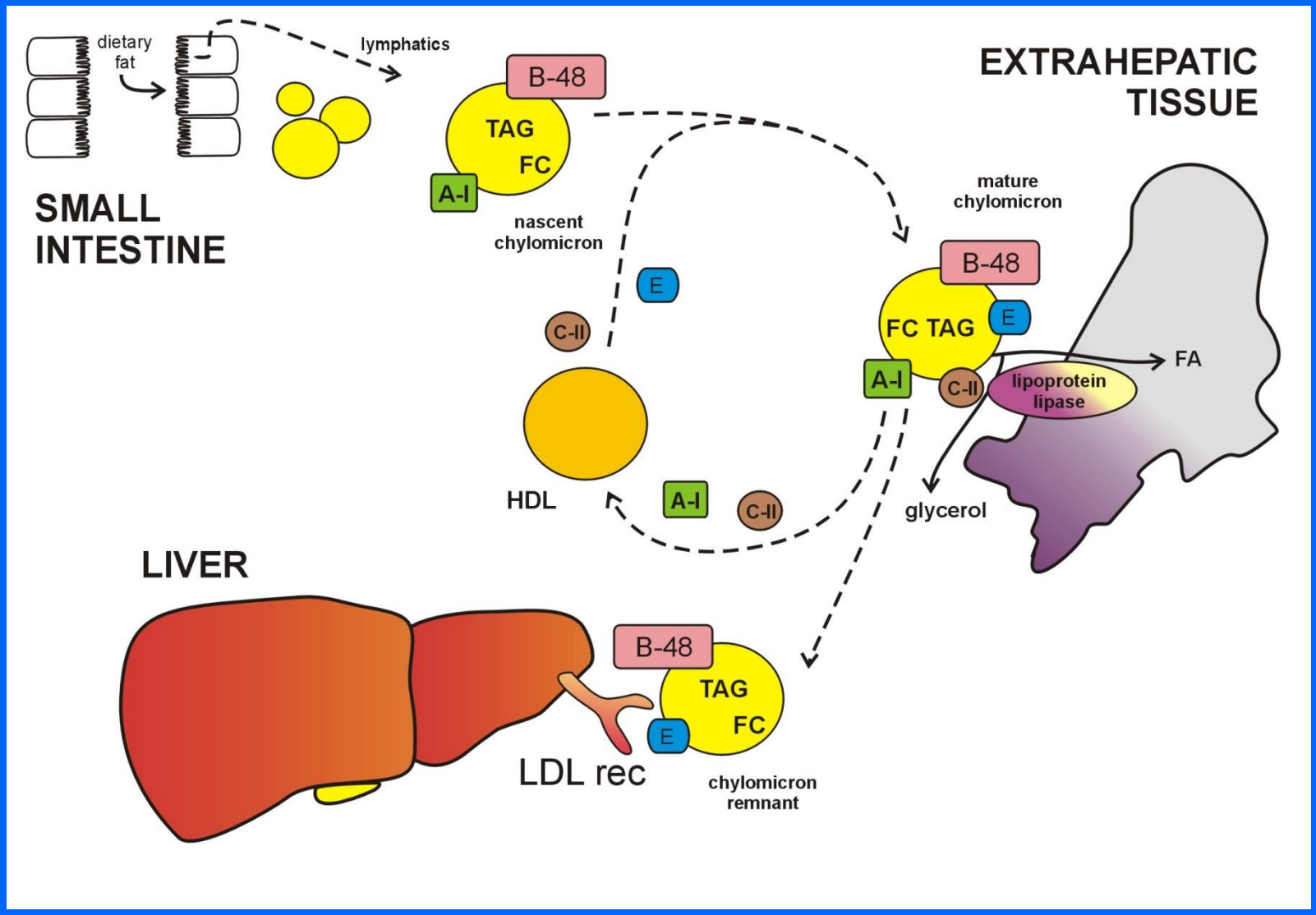
Chylomicrons



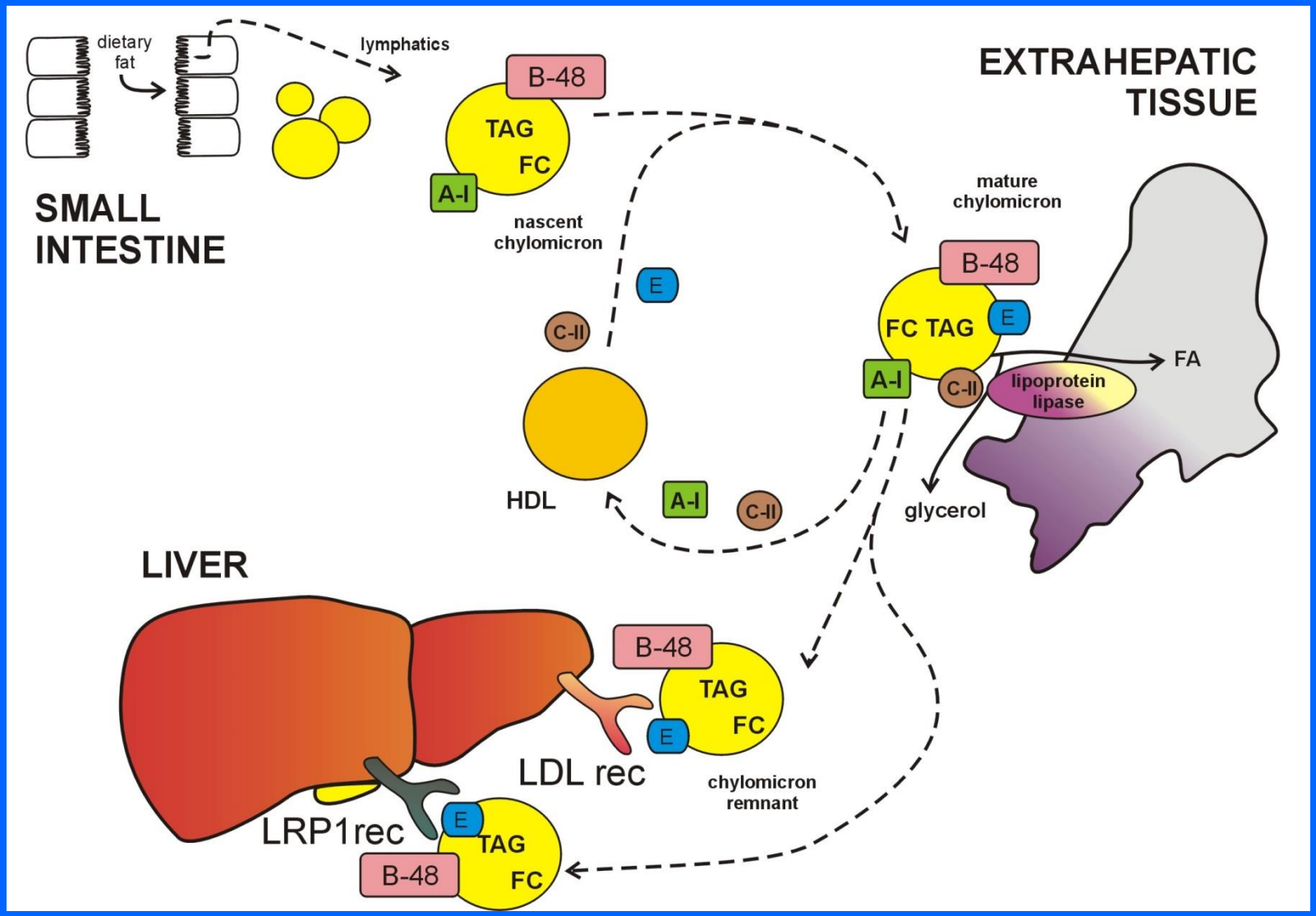
Chylomicrons



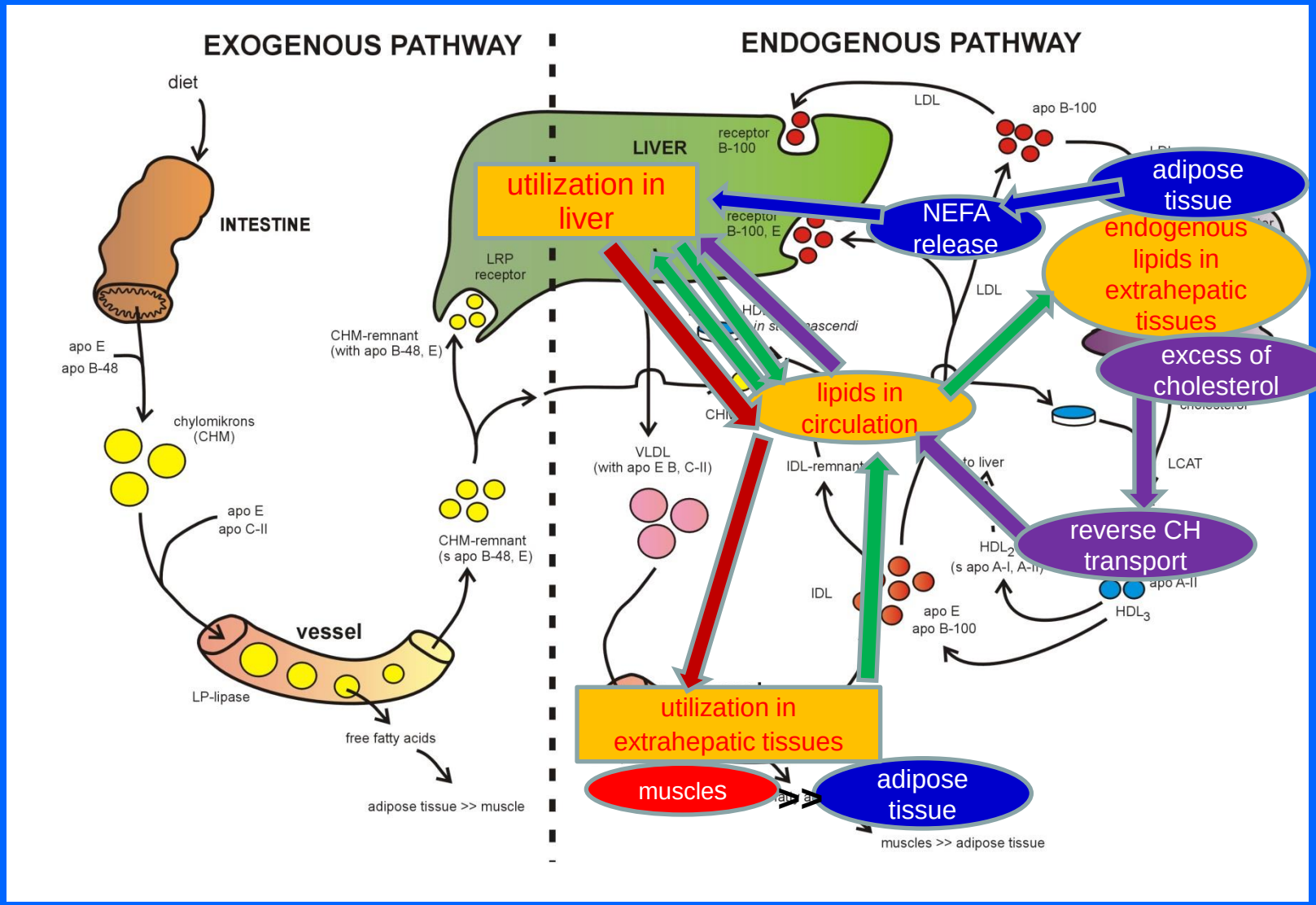
Chylomicrons



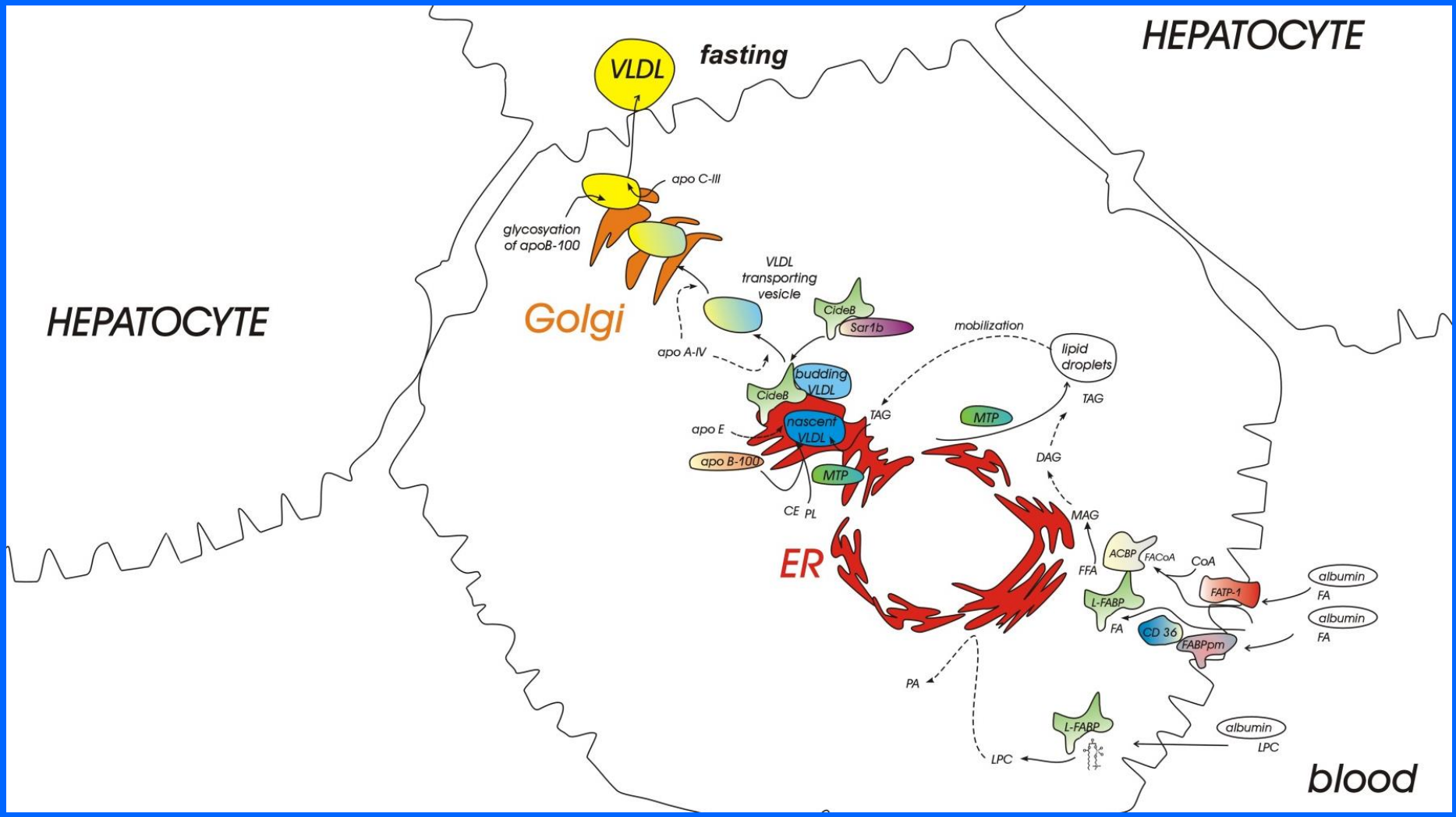
Chylomicrons



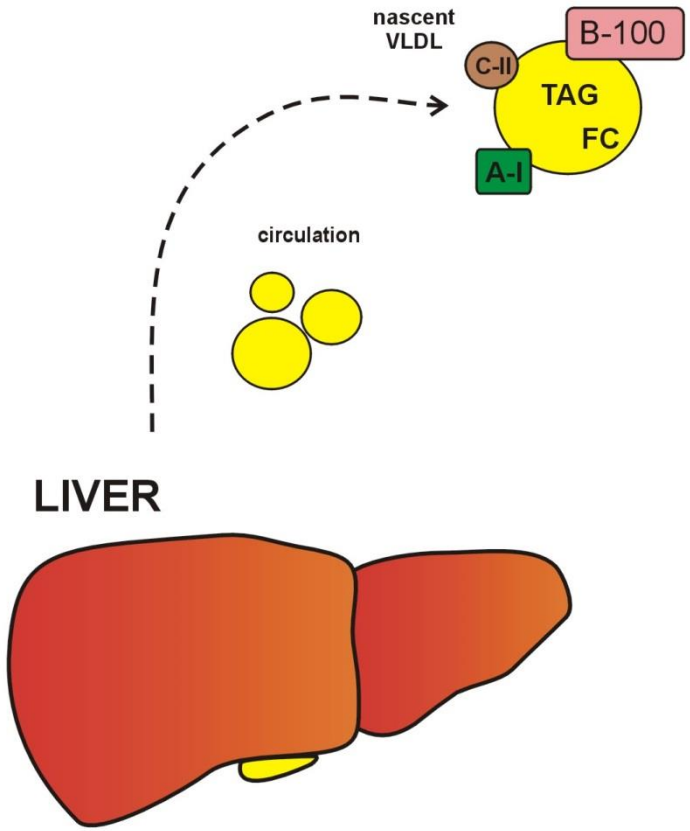
Metabolic lipoprotein pathway



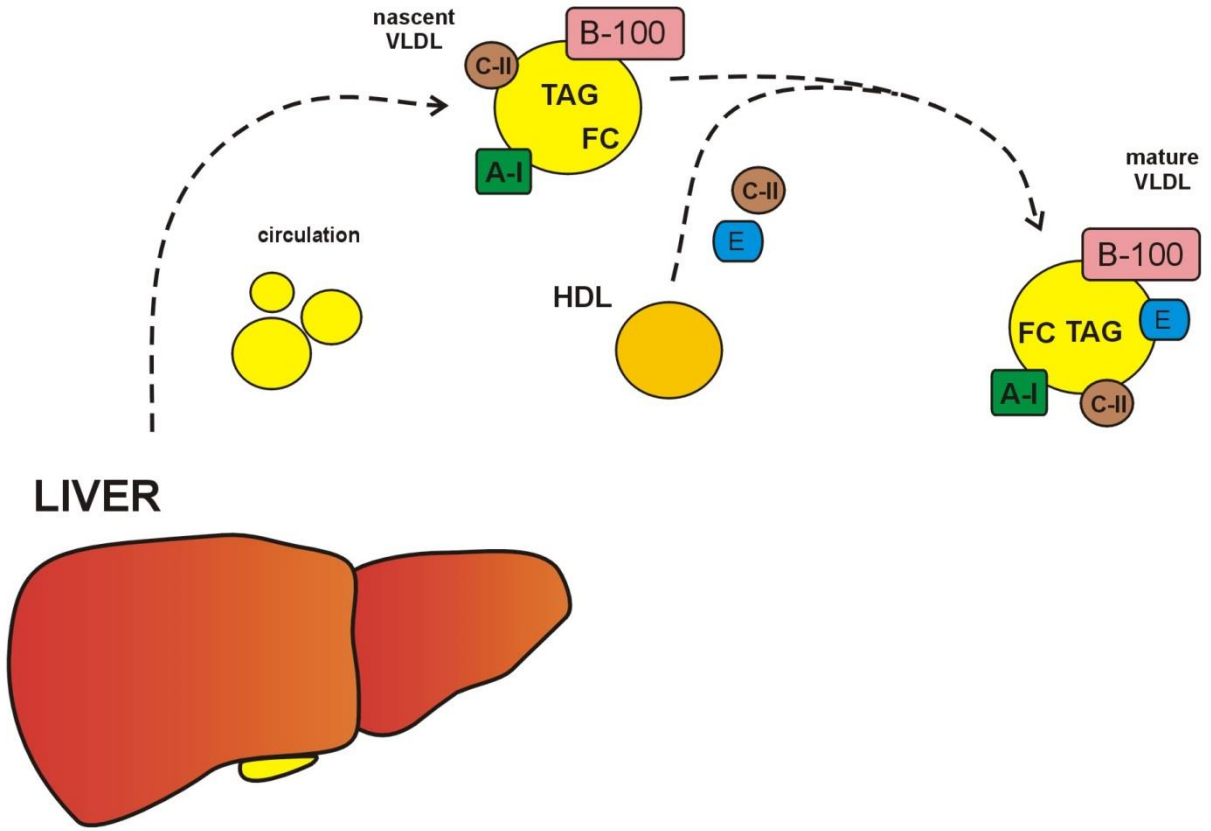
Assembly of VLDL



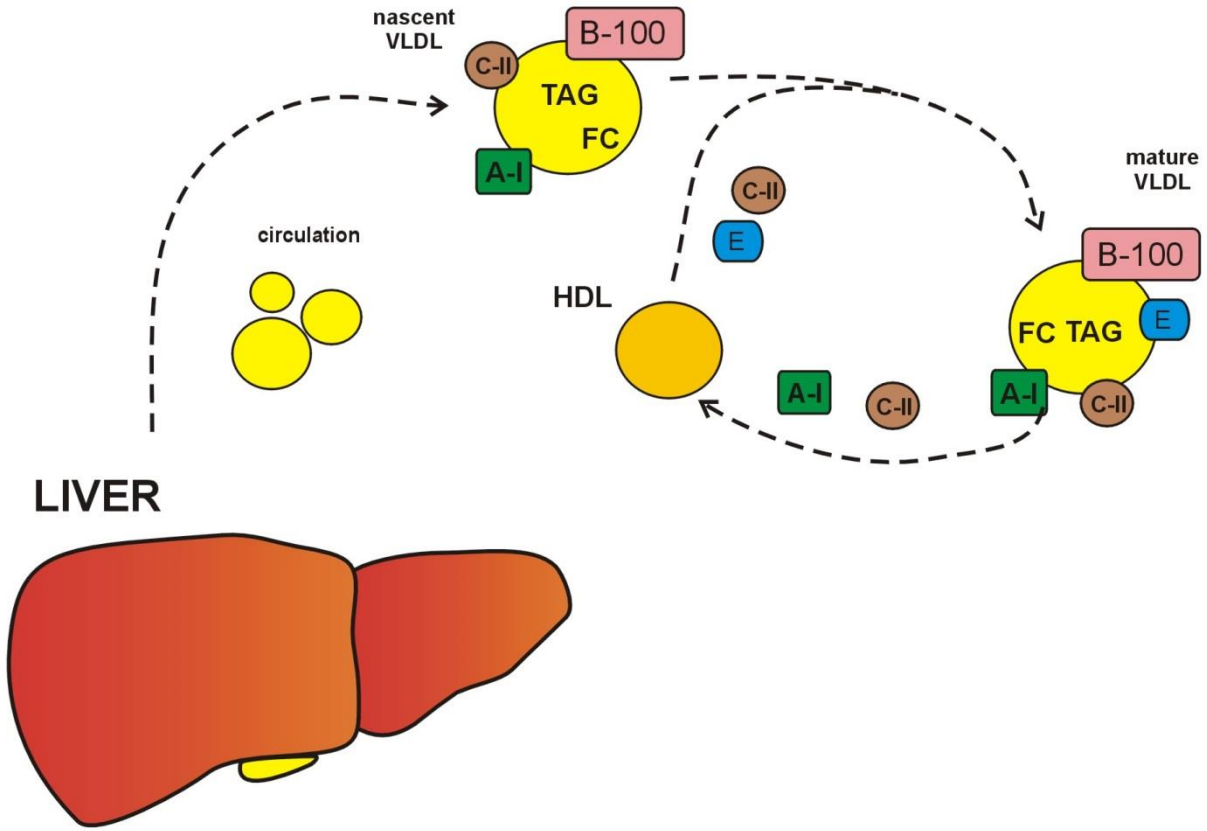
Fate of VLDLs



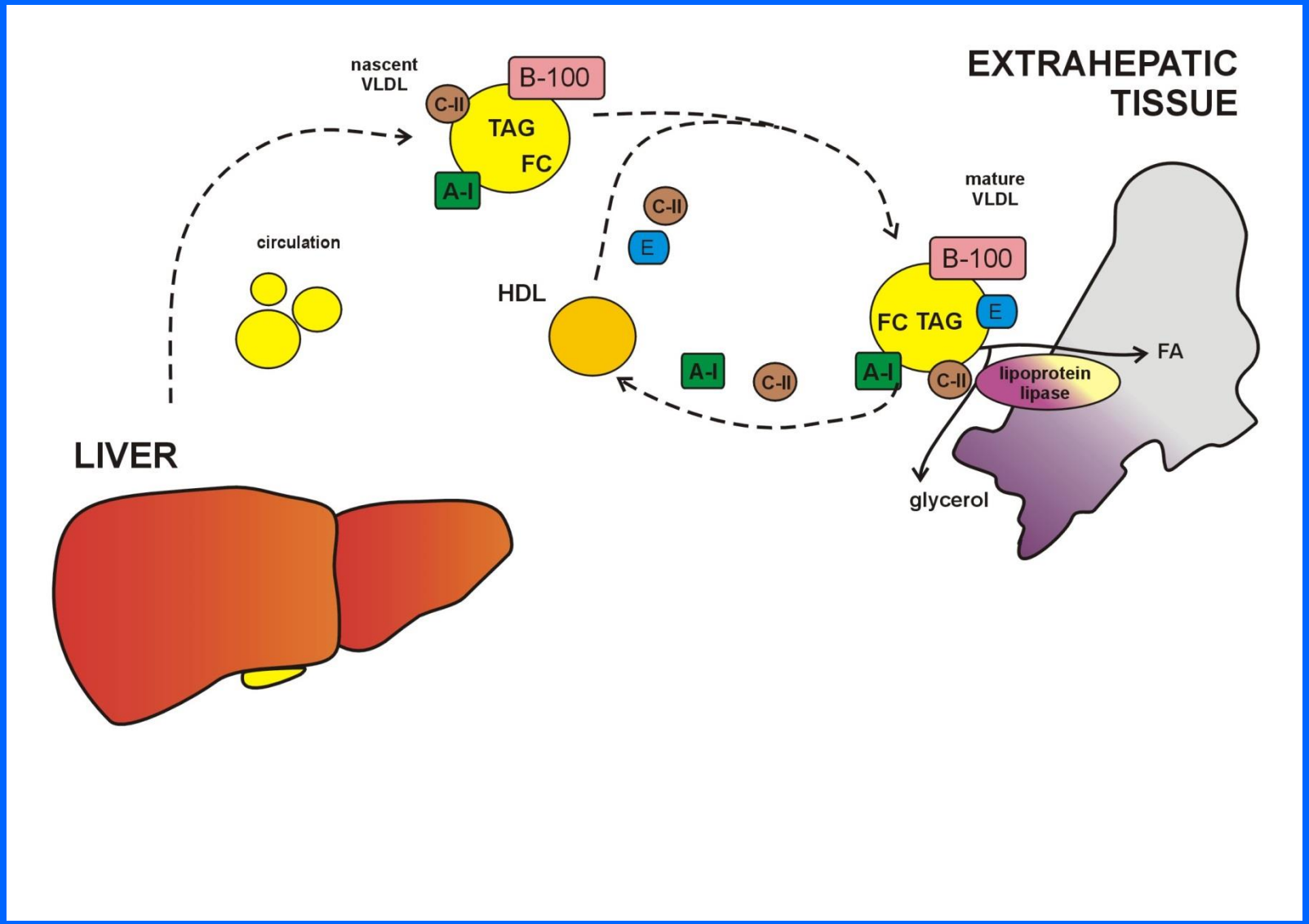
Fate of VLDLs



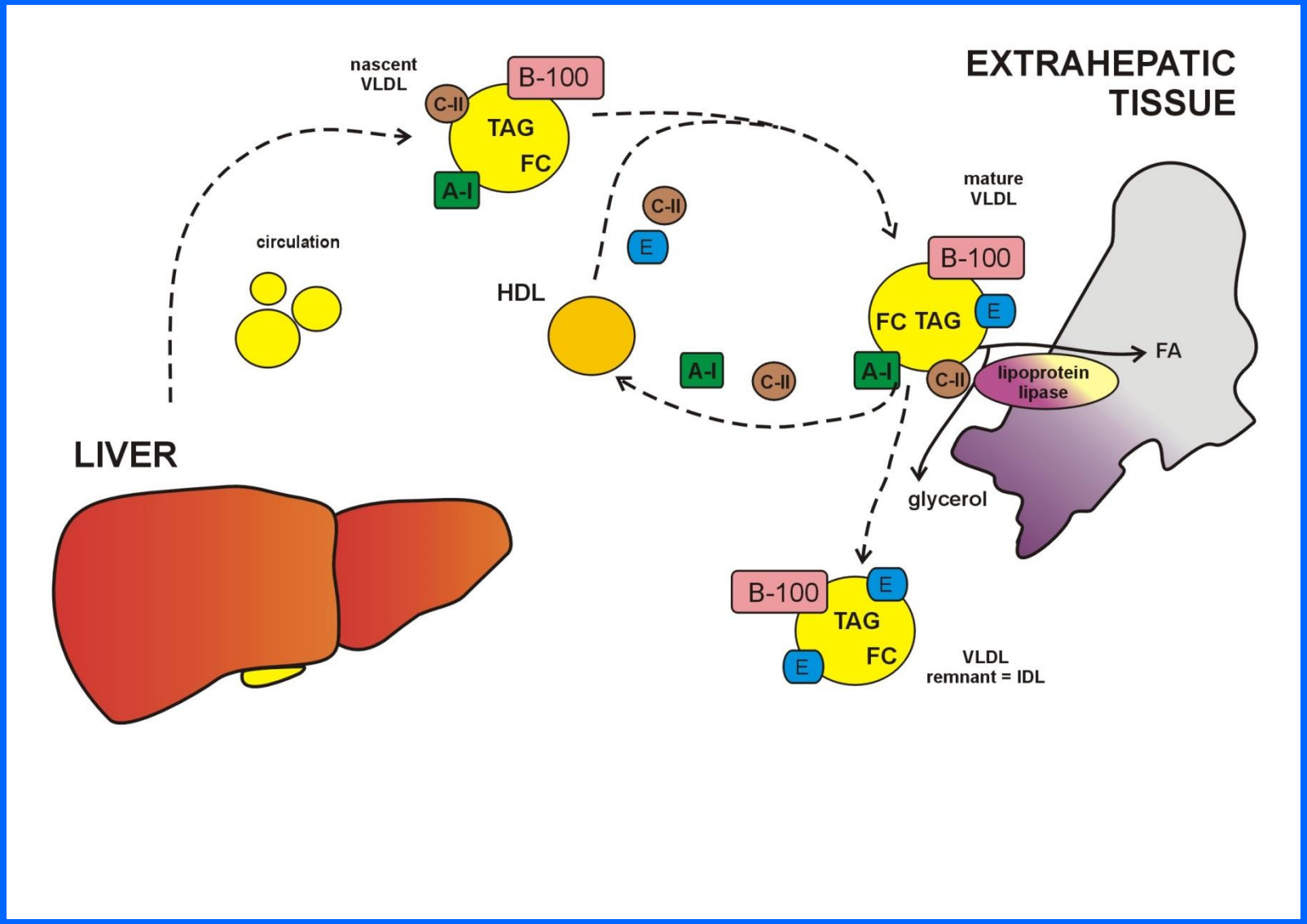
Fate of VLDLs



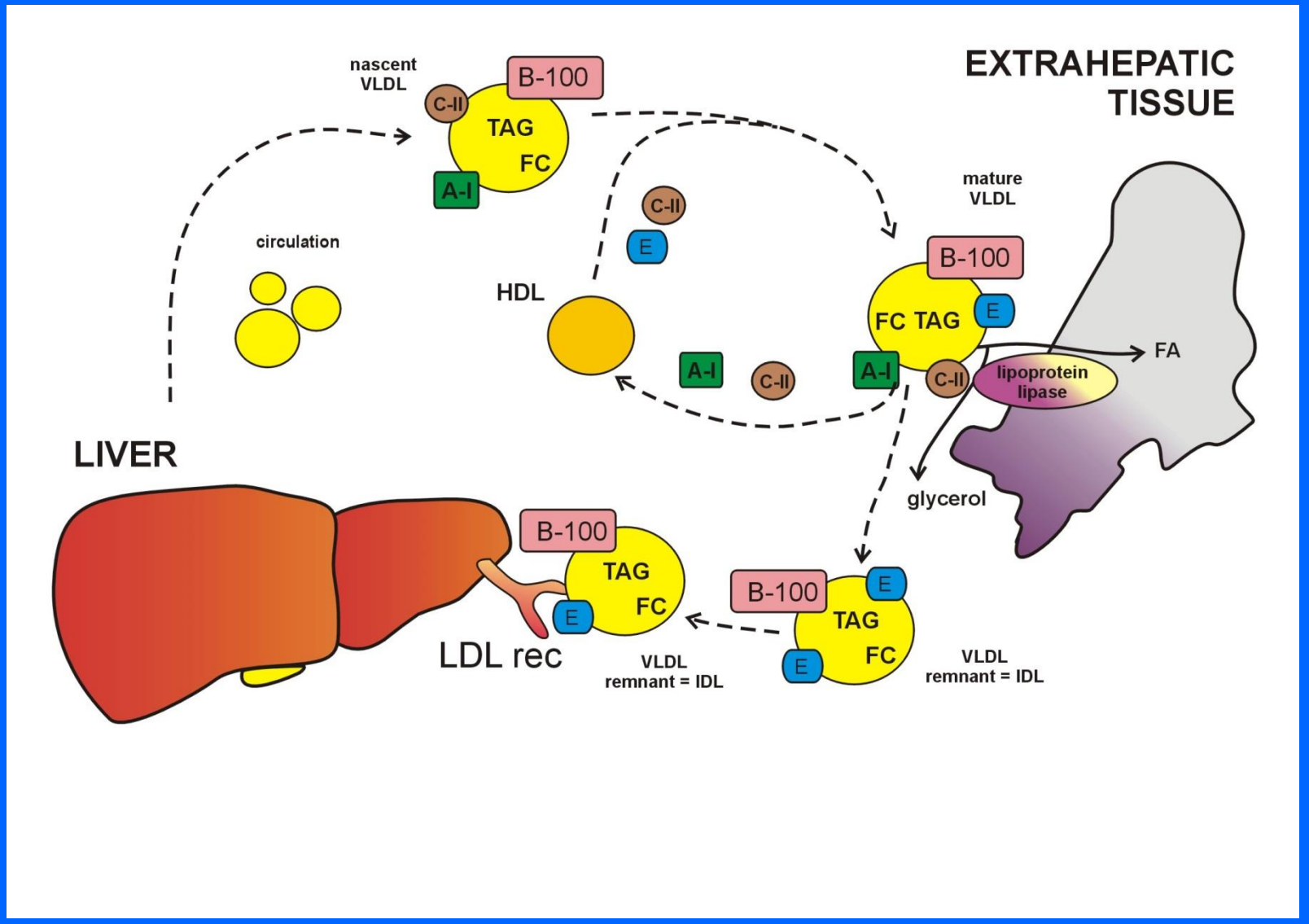
Fate of VLDLs



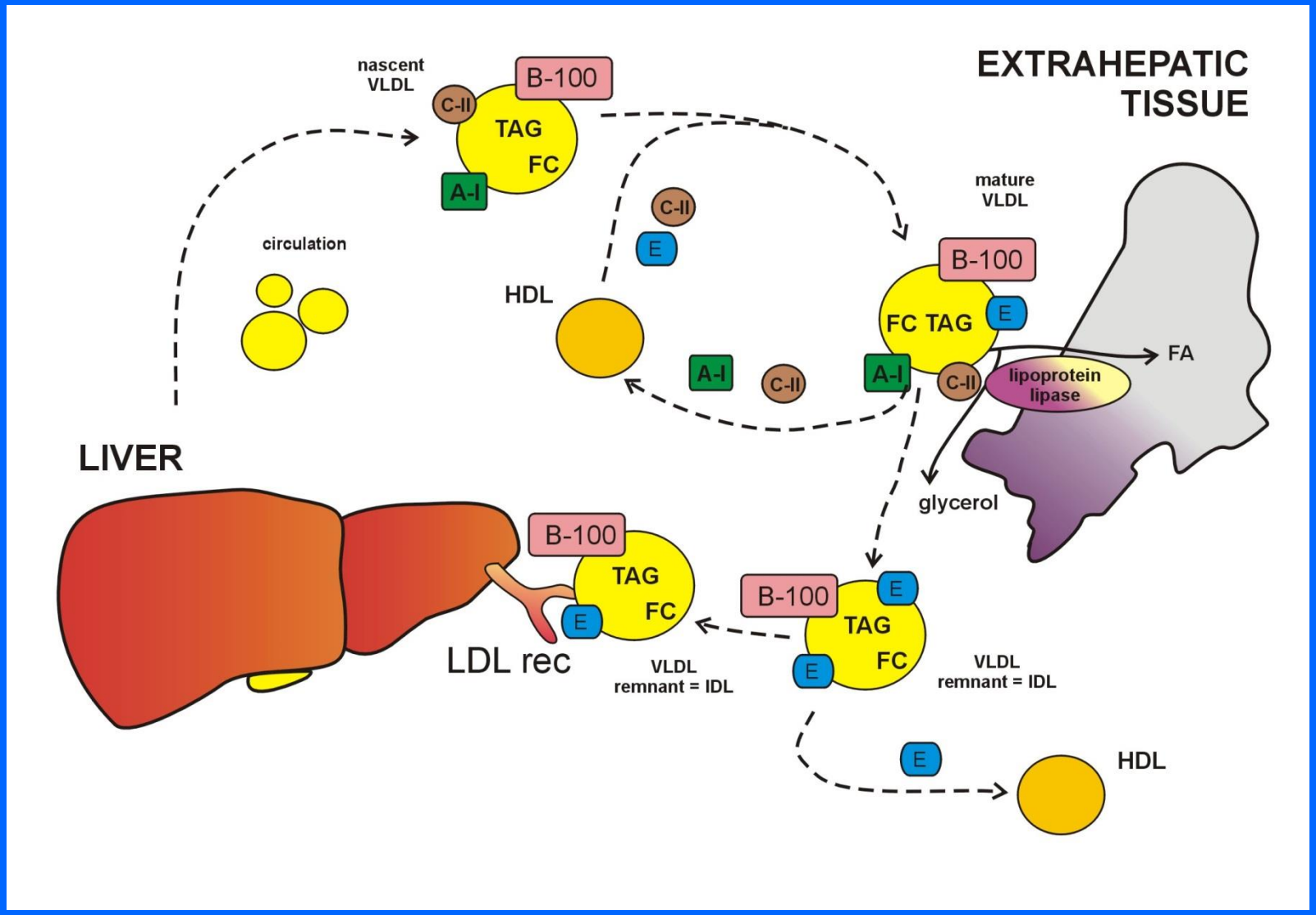
Fate of VLDLs



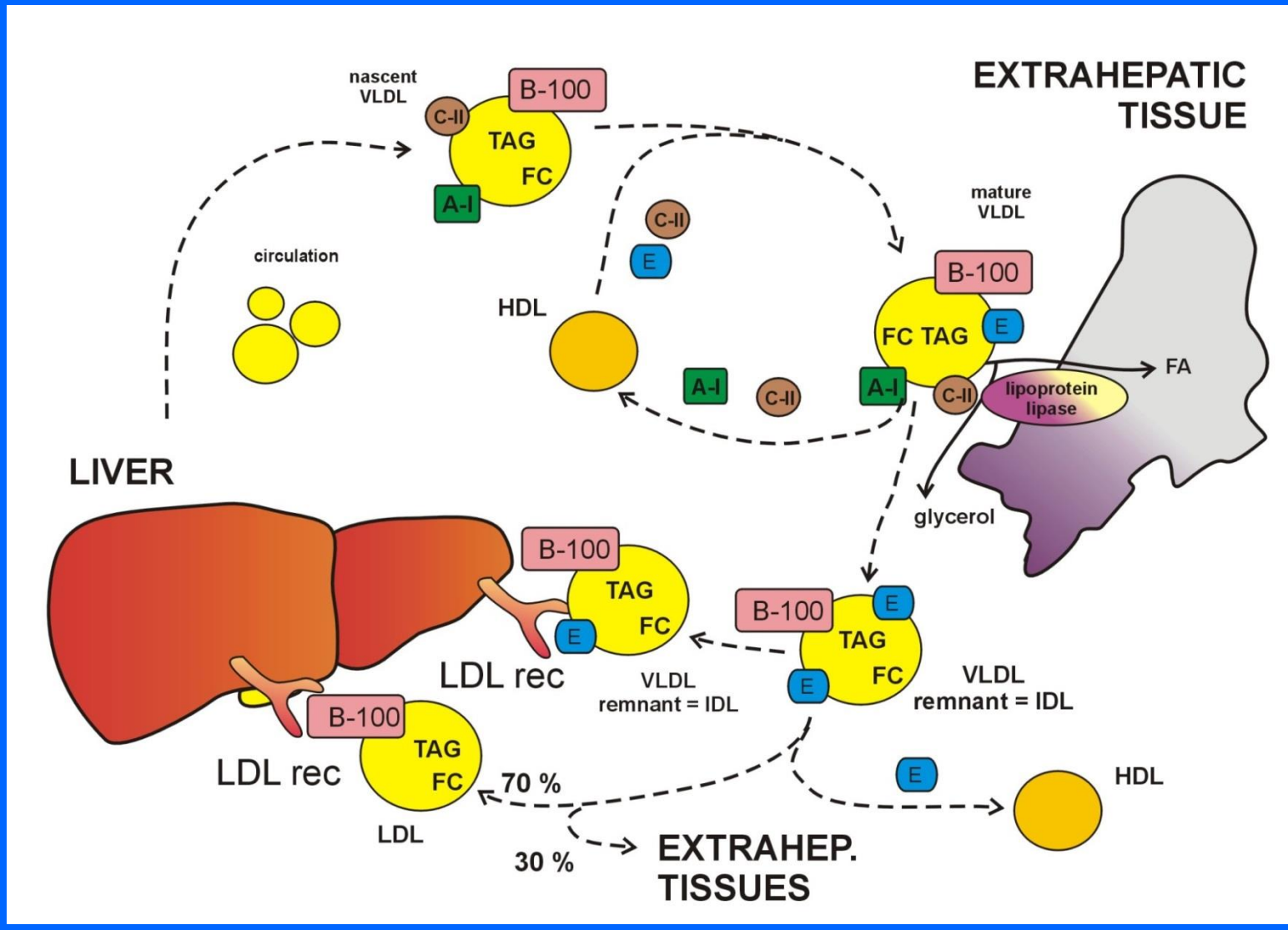
Fate of VLDLs



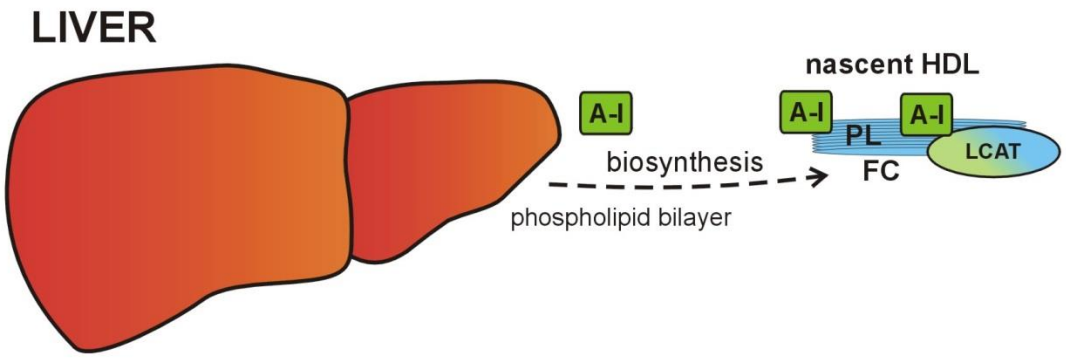
Fate of VLDLs



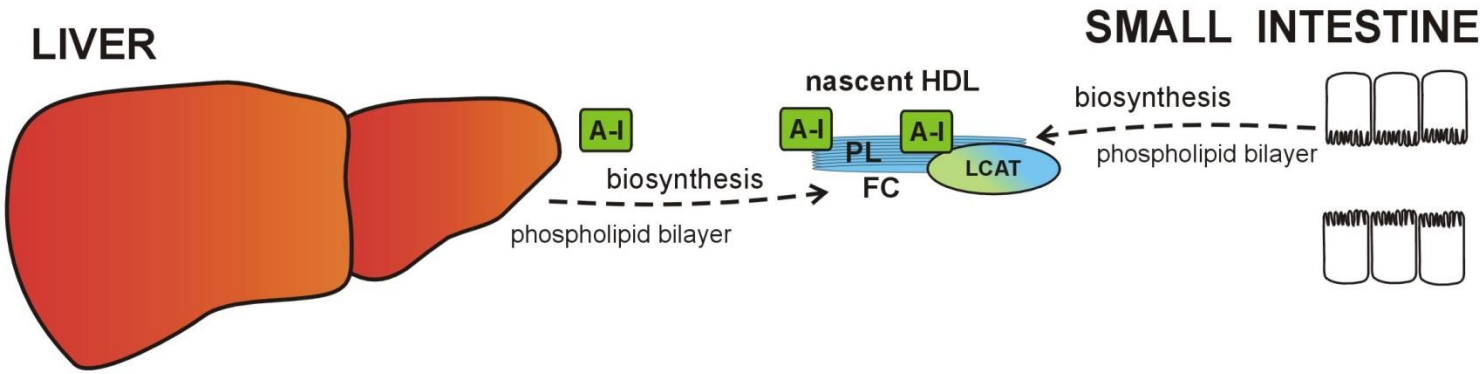
Fate of VLDLs



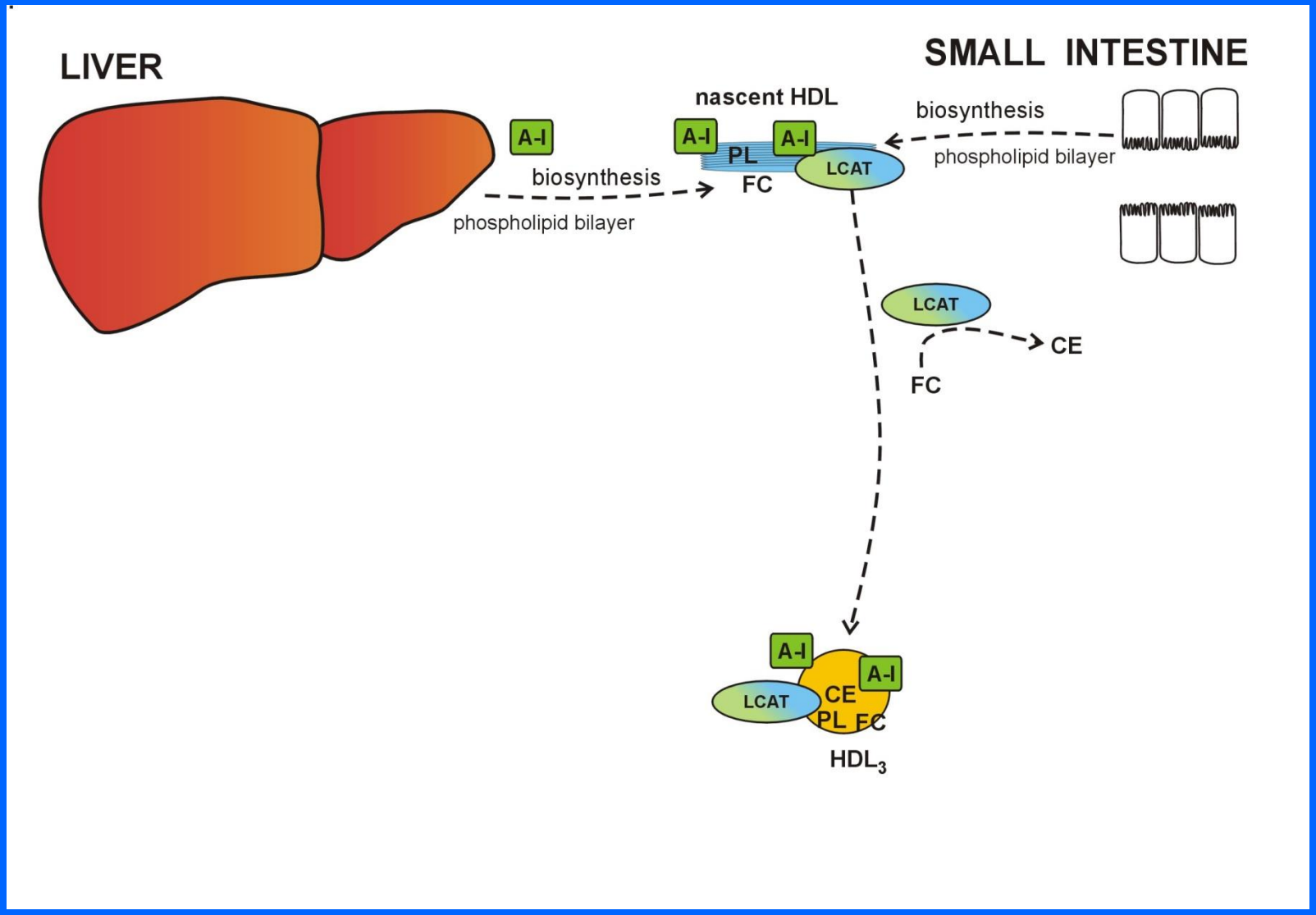
HDL and reverse cholesterol transport



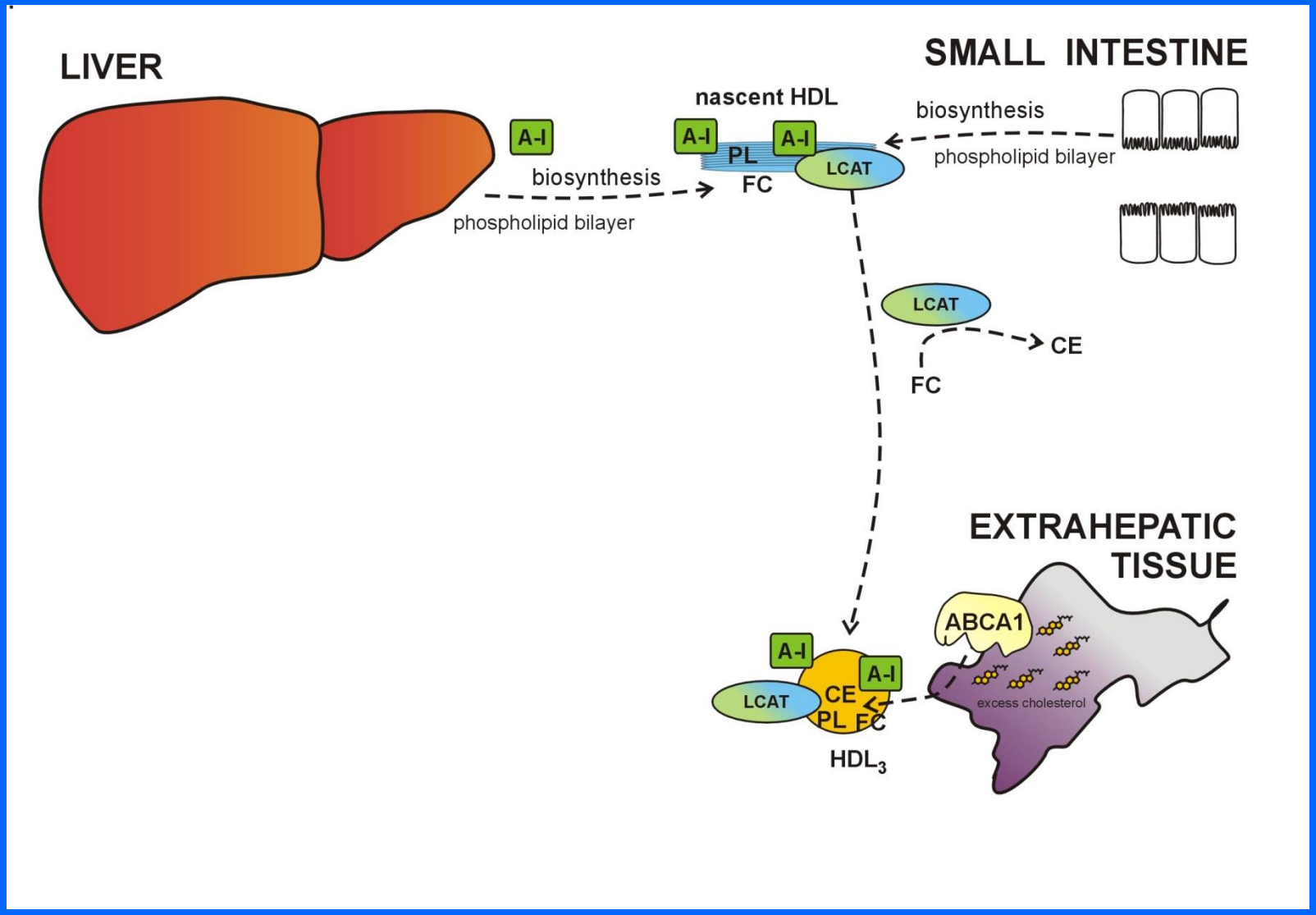
HDL and reverse cholesterol transport



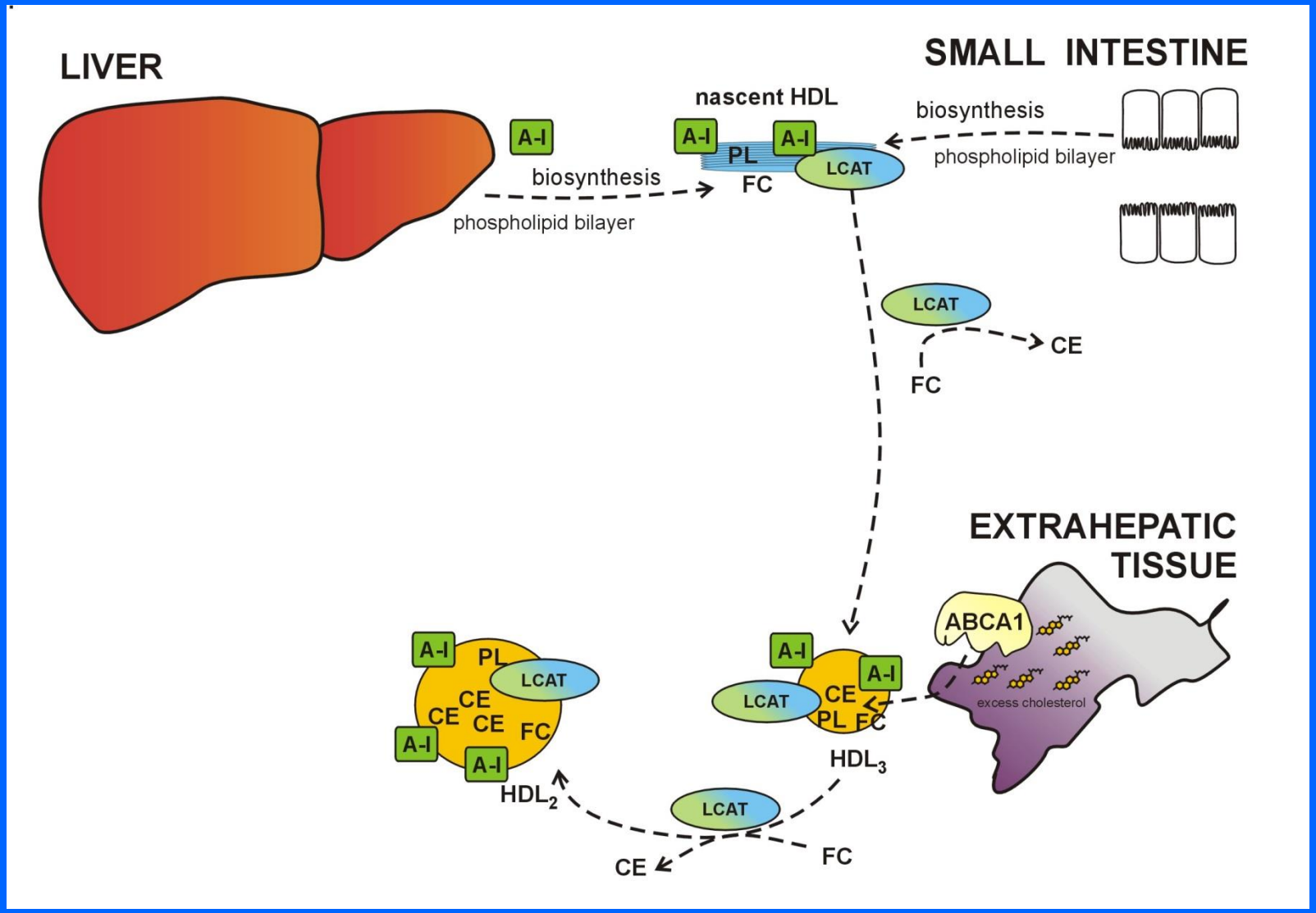
HDL and reverse cholesterol transport



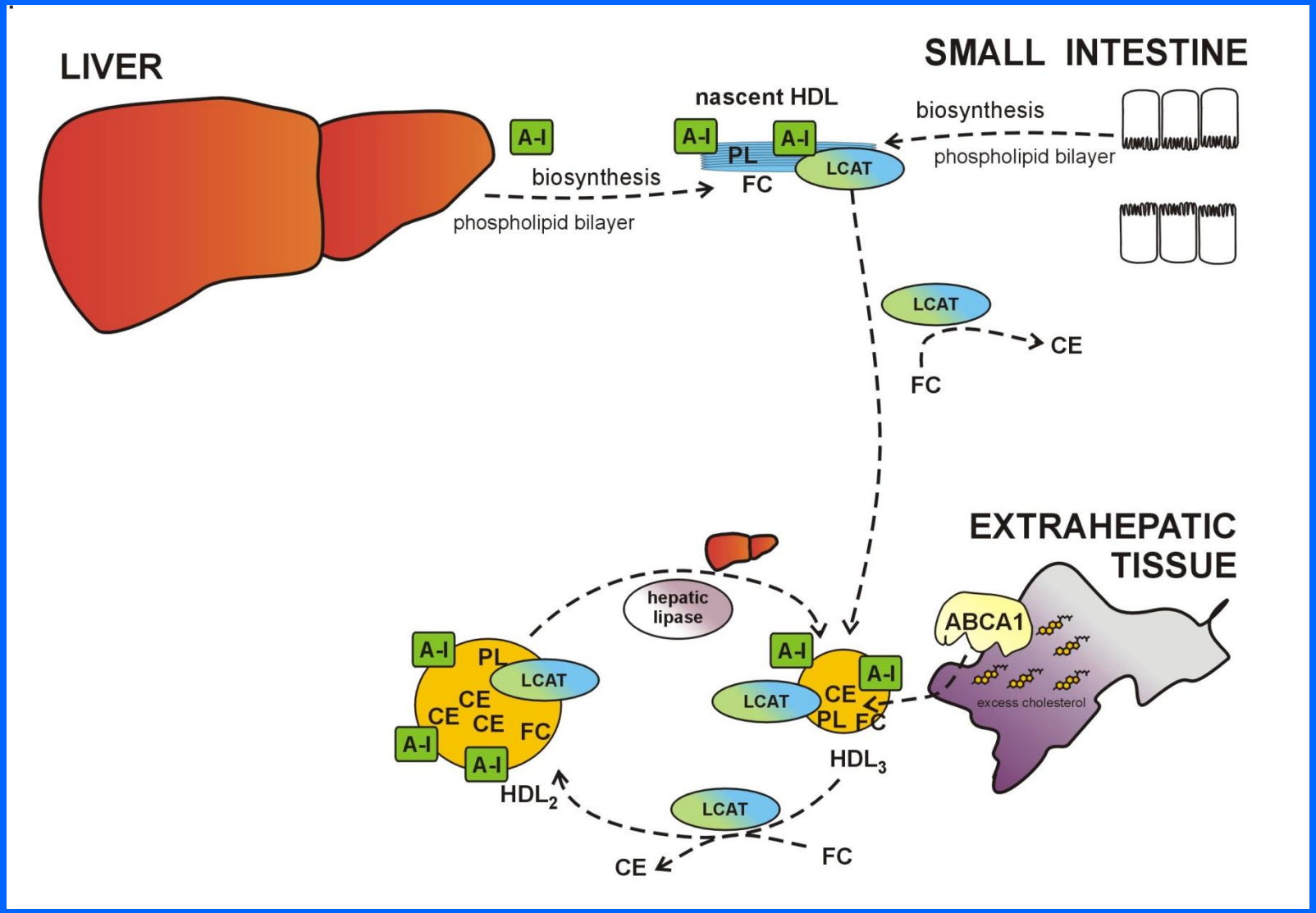
HDL and reverse cholesterol transport



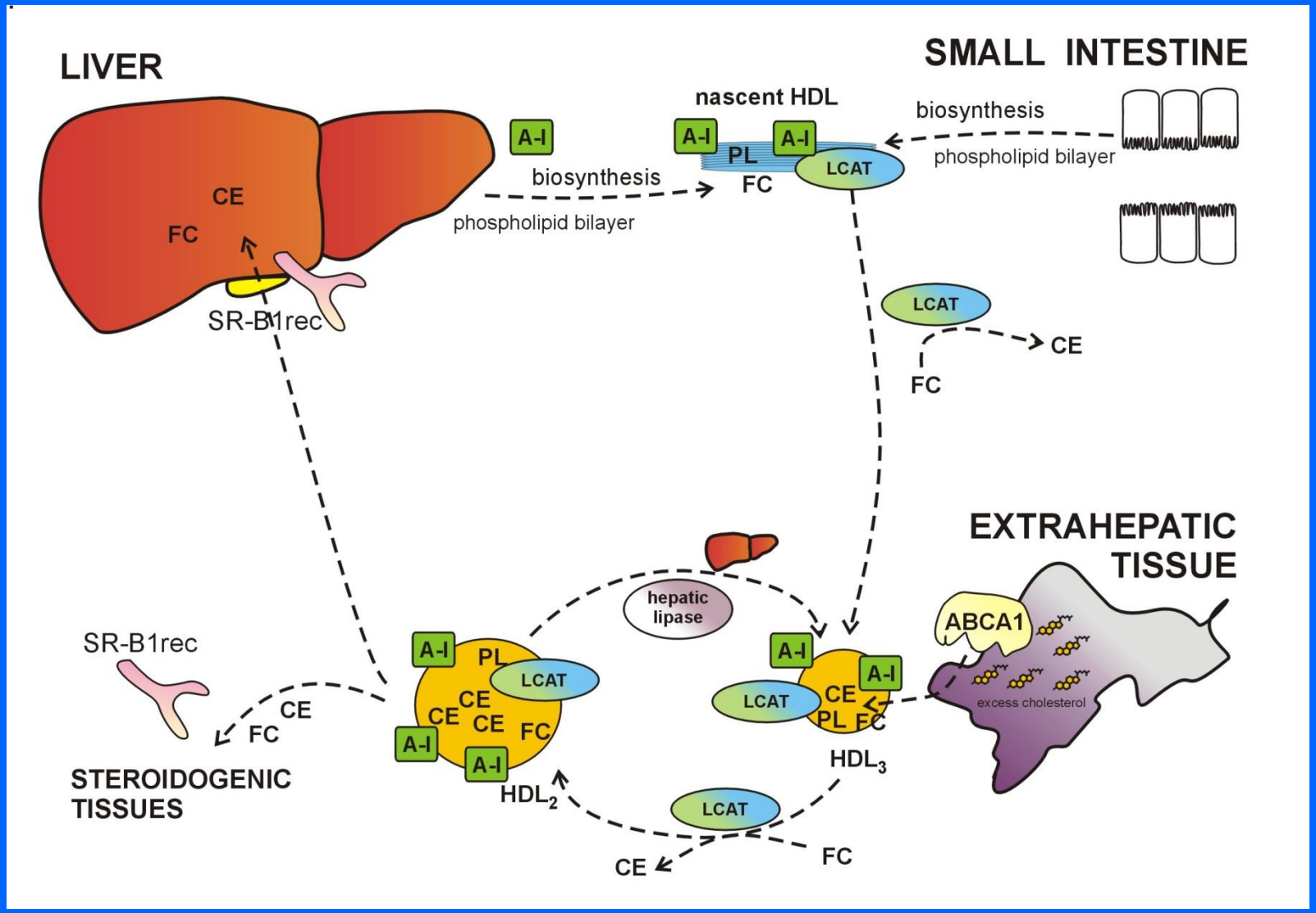
HDL and reverse cholesterol transport



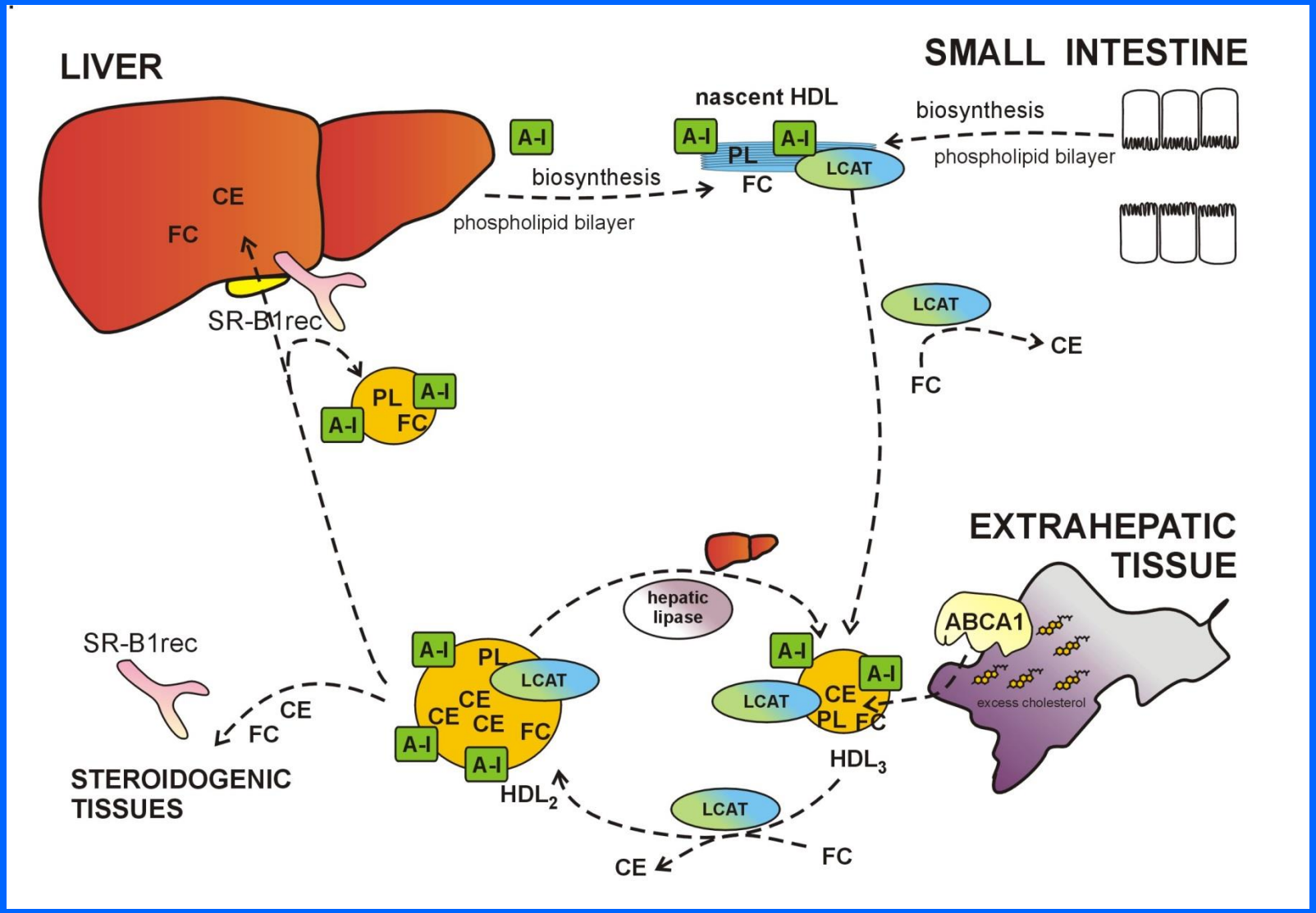
HDL and reverse cholesterol transport



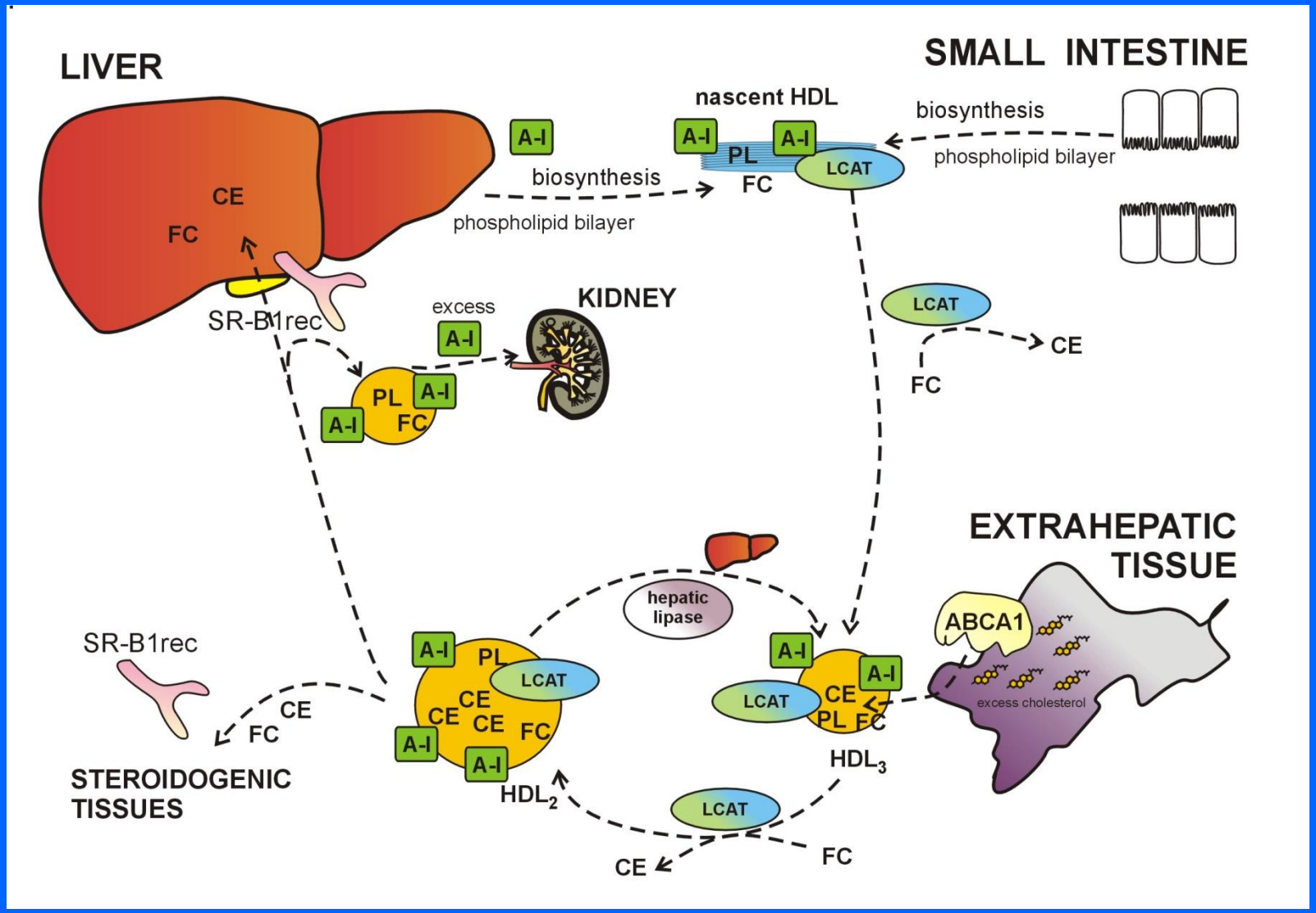
HDL and reverse cholesterol transport



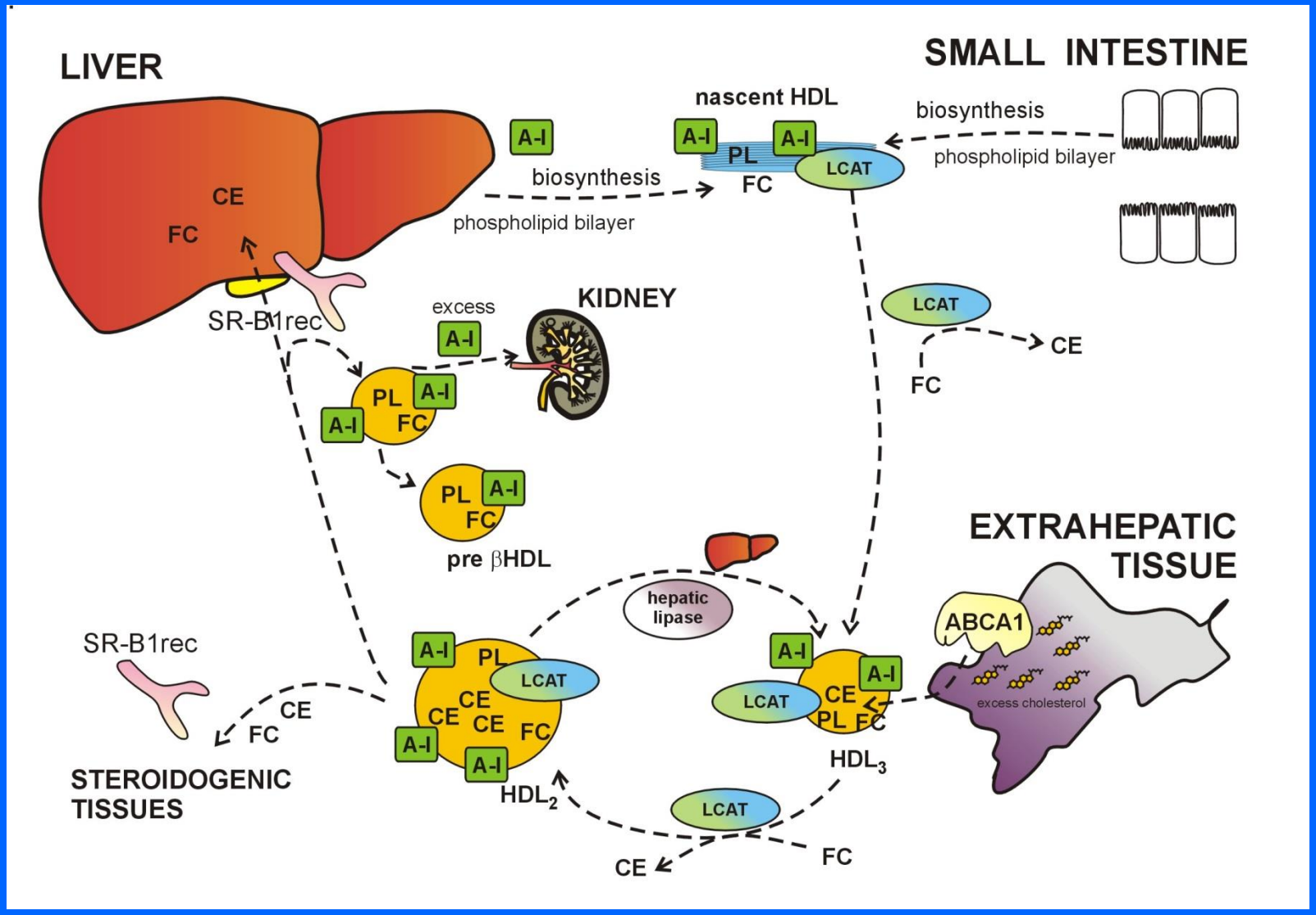
HDL and reverse cholesterol transport



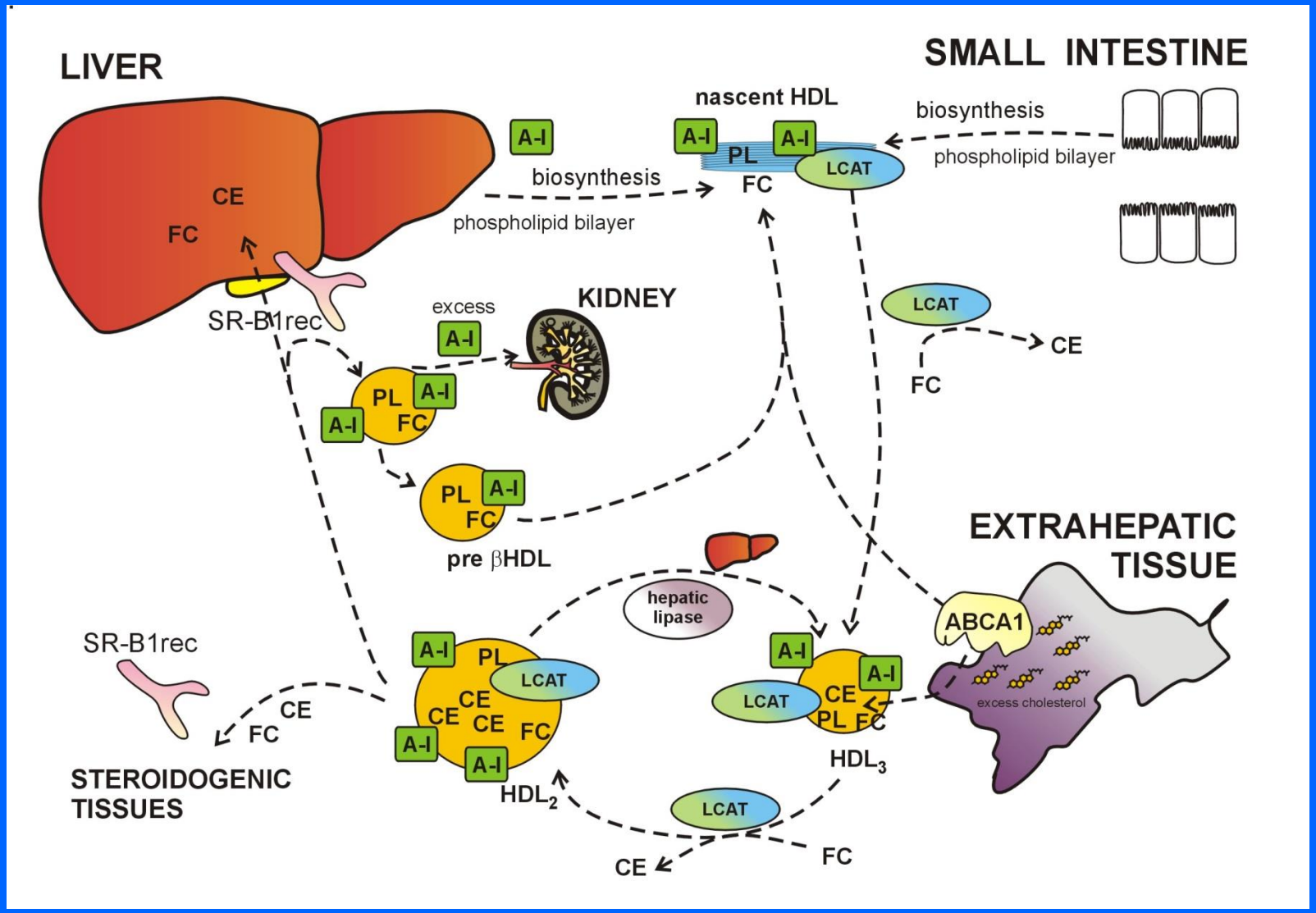
HDL and reverse cholesterol transport



HDL and reverse cholesterol transport

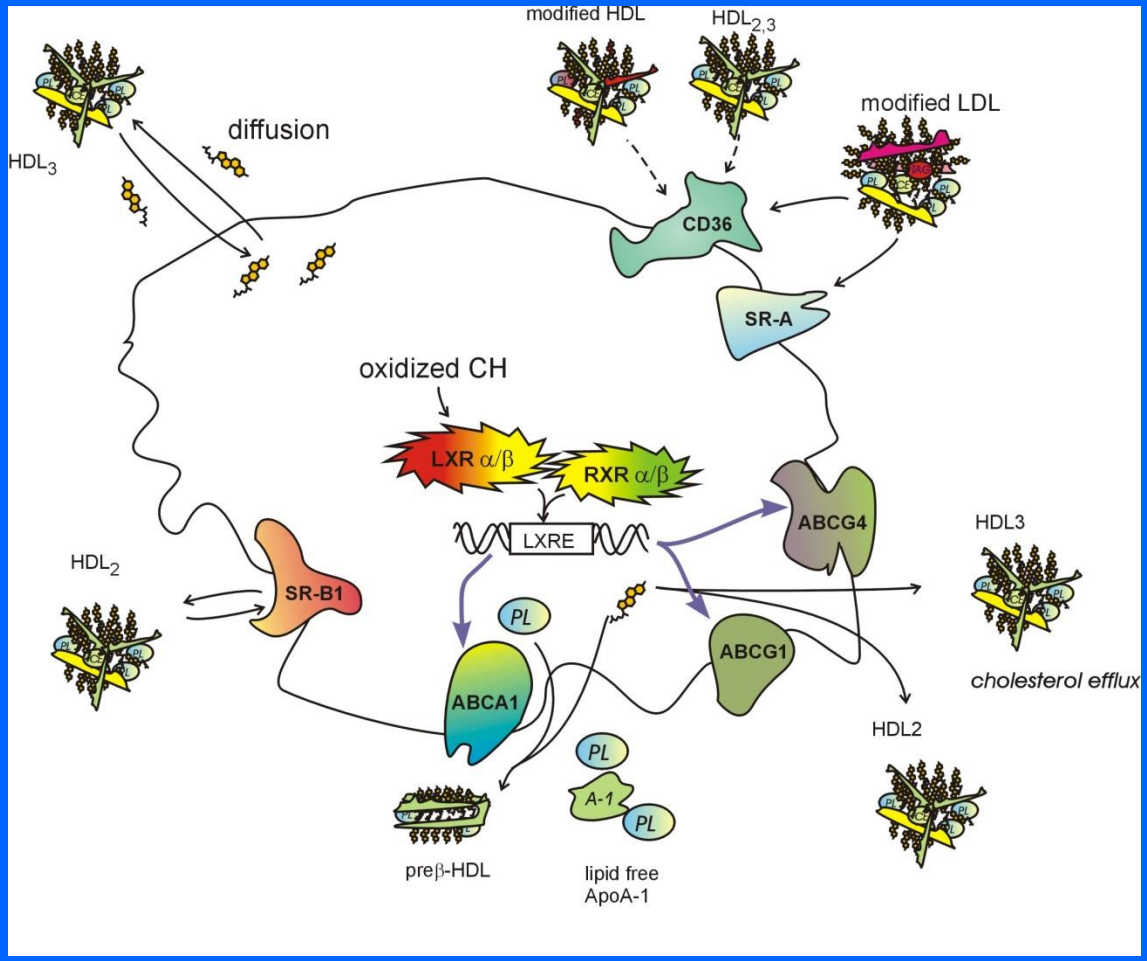


HDL and reverse cholesterol transport



Reverse cholesterol transport

sterol transport from macrophages



Other roles of HDL

Exchanges of lipid classes

- facilitating reverse cholesterol transport (LCAT)
- TAG depletion of VLDL/LDL rich particles (CETP)
- remodelling of HDLs (PLTP)

Antioxidant properties

oxPL (LDL) → oxPL (HDL)

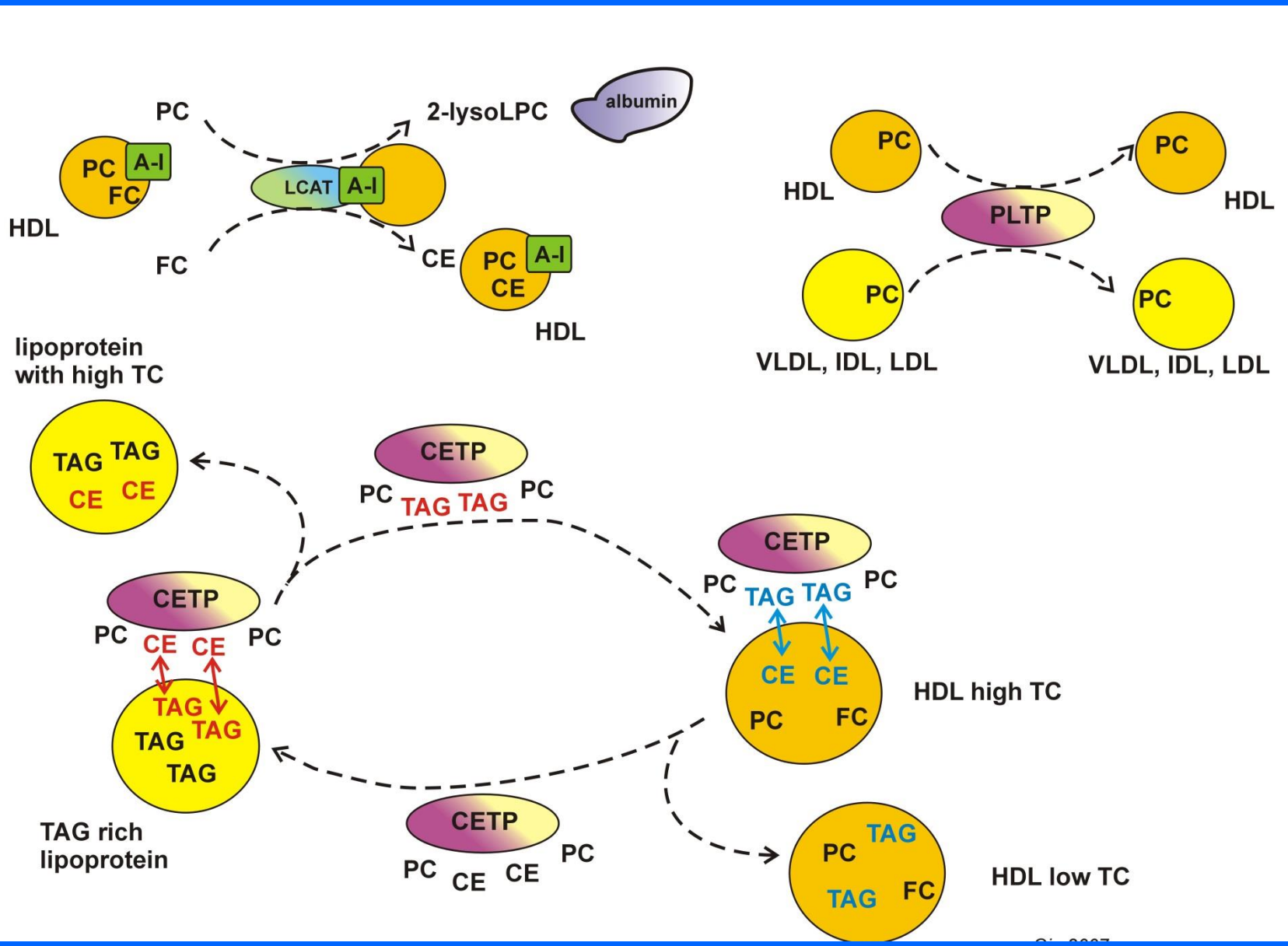
- liberation of oxidized FA from oxPL molecules (PON-1, PAF-AH)

Particle remodelation

- part of acute phase response (SAA for PON-1)

Antiinflammatory/antithrombotic vasodilatory activity

Exchanges of lipid classes



HDL and oxidative stress

1. Removal of oxidised PL from LDL (oxLDL)

oxPL (LDL) → oxPL (HDL)

sdHDL are easy acceptors for oxPL (oxLDL/membranes)

2. Inactivation of oxidised PL

- *via* redox active residues in apo A-I (Met)

  PLOOH → PLOH

- *via* liberation of oxidized FA from oxPL molecules

  paraoxonase (PON-1)

  hydrolysis of oxPUFA from oxPL/oxCE

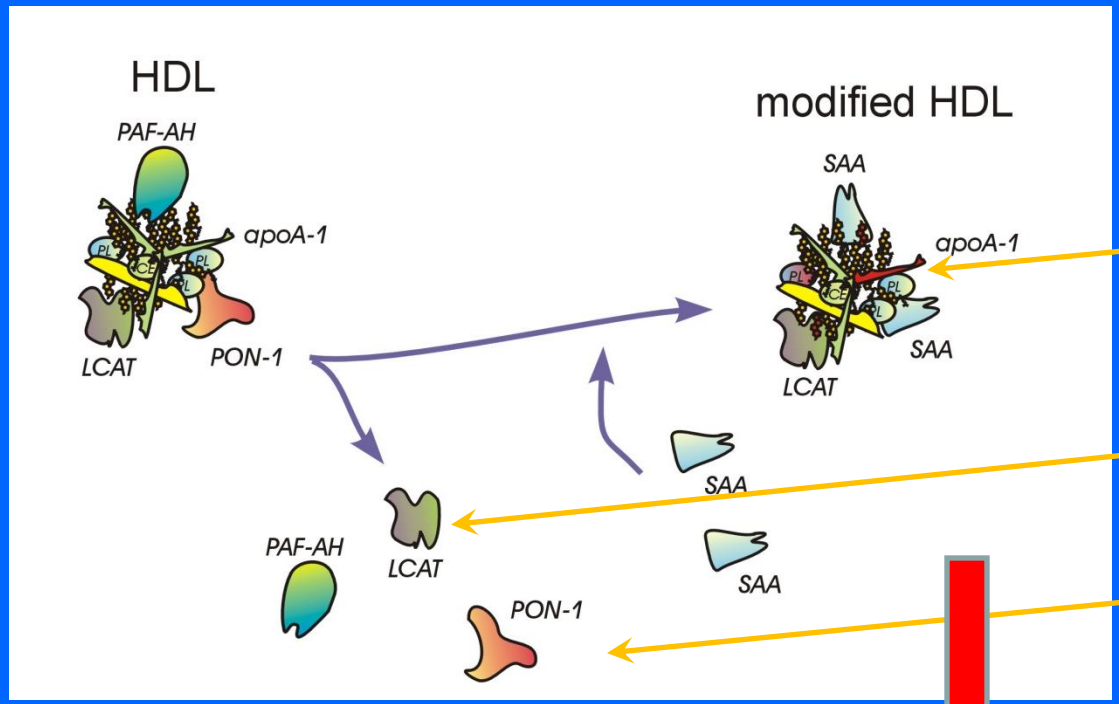
  platelet-activating factor acetylhydrolase (PAF-AH)

  hydrolysis of short chain oxFA from *sn*-2 position in ox PL

HDL remodelation

functionally defective HDL particles

acute phase response/inflammation



modification by glycation oxidation

decreased capacity for RCT

decreased antioxidant capacity of HDL

HDL particles lacking antiatherogenic functions

DISORDERS OF LIPOPROTEIN METABOLISM

DEFINITION AND SIGNIFICANCE OF DISORDERS OF LP METABOLISM

CLASSIFICATION

I. According to changes in lipid/lipoprotein classes:

a) hyperlipoproteinemia (HLP)

b) dyslipoproteinemia (DLP)

II. According to the cause:

a) primary HLP/DLP - independent, genetically determined diseases (60 - 90 %)

b) secondary HLP/DLP - consequence of disease (state) altering metabolism of LP

Definition of hyperlipoproteinemia, hyperlipidemia and dyslipoproteinemia

Hyperlipoproteinemia

= state connected with elevation of one or more LP classes

Hyperlipidemia

= state, when concentrations of TC and/or TAG exceed borderline concentration [defined by 90/95th percentiles]

Dyslipidemia

a) = state, characterised by lowered concentration of HDL-C
HDL-C ≤ 0.9 mmol/l in M (resp. 1.10 mmol/l for F)

b) more generally, any disorder of LP

Pathogenesis of lipoprotein disorders

I. ↑ synthesis of cholesterol and/or triacylglycerols → ↑ secretion of LP

II. disturbed metabolism of lipoproteins

- changes in remodelation of particles → abnormal composition:

LP-X (liver cirrhosis), small dense LDL

- ↓ catabolism of lipoproteins

III. combination of abovementioned mechanisms

+ interaction of genetically susceptible background and non genetic effects (nutritional, metabolic, disease states)

Classification of phenotypes of hyperlipoproteinemias

Primary HLP

Phenotype	Lipoprotein cholesterol					Primary cause
	CM	VLDL	IDL	LDL	HDL	
I	↑			↓	↓	deficiency/inhibitor of LPL deficiency of apo C-II deficient apo A-V, LMF1
IIA				↑		FHC, FCH, PHC, deficient B-100
IIB		↑		↑↑		FCH, FHC
III	↑ (CH-R)	b-VLDL	↑			familial HLP III type familial deficiency of HL
IV		↑			↓	FHTG (polymorphisms of LPL) polymorphisms of apo A-V
V	↑	↑		↓	↓	FHTG (decompensation) deficiency of apo C-II, A-V

LPL – lipoprotein lipase, LMF1 – lipase maturation factor 1, HL – hepatic lipase, CH-R – chylomicron remnants, FHC – familial (= monogenic, "receptor") hypercholesterolemia, FCH – familial combined hyperlipoproteinemia, PHC – polygenic hypercholesterolemia, FHTG – familial hypertriacylglycerolemia

Classification of phenotypes of hyperlipoproteinemias

Secondary HLP

Phenotype	Lipoprotein cholesterol					Secondary cause
	CM	VLDL	IDL	LDL	HDL	
I	↑			↓	↓	systemic lupus erythematodes (rarely)
IIA				↑		hypothyreosis, anorexia nervosa
IIB		↑		↑↑		nephrotic syndrome, anorexia nervosa, DM
III	↑ (CH-R)	b-VLDL	↑			hypothyreosis, DM, obesity
IV		↑			↓	DM, chronic renal insufficiency
V	↑	↑		↓	↓	EtOH abuse, diuretic treatment, estrogens (hormonal contraception, hormonal replacement therapy)

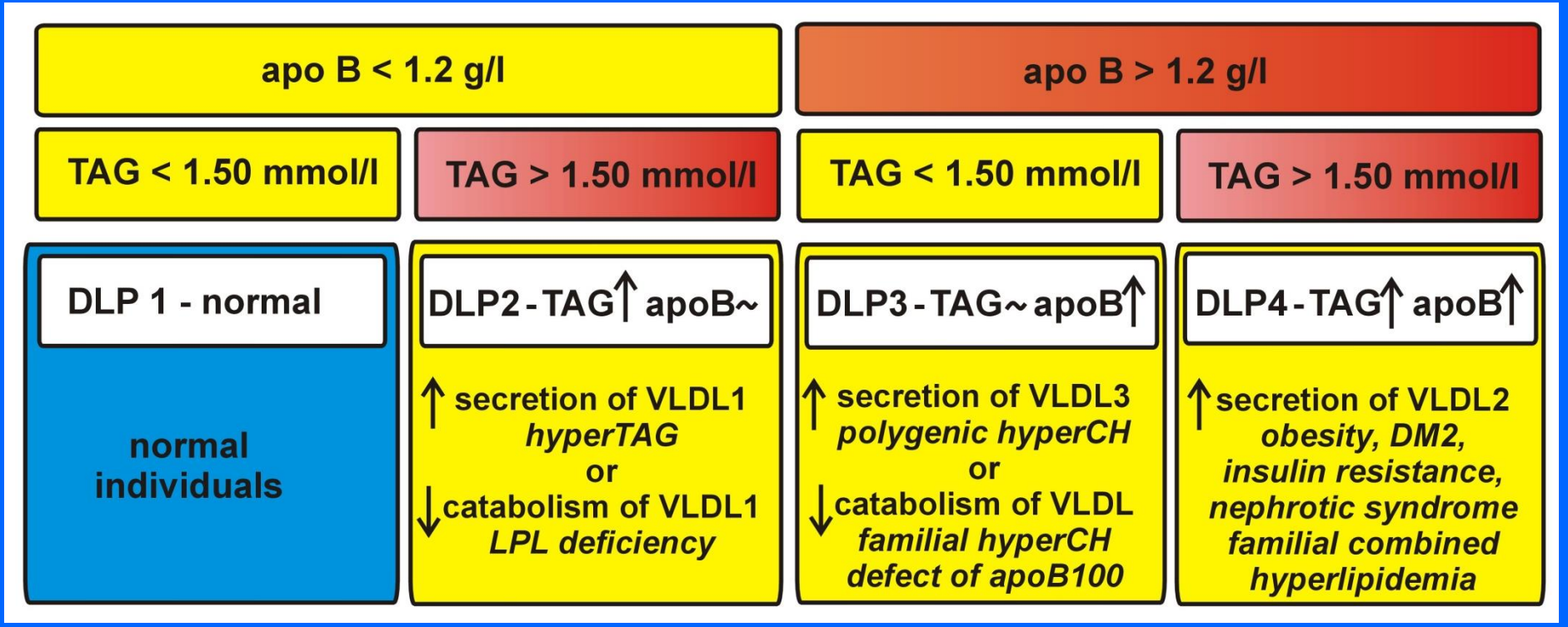
DM – diabetes mellitus

Present classification of hyperlipidemias

Type of hyperlipidemia	Disorder in lipoprotein class	Example
Hypercholesterolemia	LDL rarely HDL	Familial(monogenic) hypercholesterolemia Polygenic hypercholesterolemia Hyperalfacholesterolemia
Hypertriacylglycerolemia	VLDL rarely VLDL + CM rarely CM	Familial endogenous hypertriacylglycerolemia Familial mixed hypertriacylglycerolemia Familial hyperchylomicronemia
Mixed hyperlipidemia	VLDL + LDL rarely IDL	Familial mixed hyperlipidemia Familial dysbetalipoproteinemia Familial hepatic lipase deficiency

LDL – low density lipoproteins, VLDL – very low density lipoproteins, CM - chylomicrons, IDL – intermediary density lipoproteins, HLP - hyperlipoproteinemia

CLASSIFICATION OF DISTURBED LIPID METABOLISM by Sniderman



VLDL1, VLDL2, VLDL3 – subpopulations of VLDL particles

Low concentration of HDL-cholesterol

Genetic factors

- deficiency/abnormal structure of apo-A-I (e.g. Apo A-I $_{Milano}$)
- Tangier disease (deficiency of ABCA1)
- deficiency of LCAT - ”fish eye disease”
- deficiency and mutations of LPL
- cholesteryl ester storage diseases (lysosomal CEH)
- Niemann-Pick disease (A, B, C variants)

Non genetic causes

- obesity, hypertriacylglycerolemia
- renal insufficiency
- smoking
- decreased physical activity
- enhanced intake of SFA/diminished supply of PUFA n-3, PUFA n-6
- drugs (thiazides, α-methyl DOPA, spirolactone, phenothiazins)

Endocrinopathies

Hypothyreosis

➡ ↓ activity of LDL receptors and LPL (HLP IIA > IIB, III, > IV)

never phenotype HLP I and V, <10% no LP change

with E2/E2 ➡ HLP type III

relatively high frequency

(4, resp. 8 % persons with hypercholesterolemias)

Estrogens (hormonal contraception,gravidity)

➡ ↑ VLDL, ↑ LDL and ↑ HDL (FCH) (phenotype IIB, IV)

gravidity

➡ physiological secondary HLP

(estrogens, progesteron, IR, hyperinsulinaemia, human placental lactogen)

Lipid metabolism during fasting

Mobilization of lipid stores

adipose tissue

activation of HSL: TAG → glycerol + 3 NEFA

albumin

liver

gluconeogenesis *(for brain, muscles)*

ketone bodies *(for brain)*

depletion of glycogen

muscle proteins → AA

acetylCoA excess

TCA cycle intermediates (oxaloacetate) are used for gluconeogenesis

Further reading

Textbooks, monographs

Biochemistry of Lipids, Lipoproteins and Membranes (5th Ed); Vance DE, Vance Je (Eds.), Elsevier, Amsterodam (The Netherlands) 2008

Lehninger Principles of Biochemistry (6th Ed); Nelson DL, Cox MM (Eds.), Susan Winslow, New York (U.S.A.) 2013

Harper´s Illustrated Biochemistry (28th Ed); Murray RK, Bender DA, Botham KM, Kennely PJ, Rodwell VW, Weil PA (Eds.), McGraw-Hill, New York (U.S.A.) 2009

High Density Lipoproteins: From Biological Understanding to Clinical Exploitation; Eckardstein A, Kardassis D (Eds.). Springer Open, London (UK) 2015

Lipoproteins in Health and Disease; Betteridge J, Shepherd J, Illingworth R (Eds.). CRC Press, London (UK) 1999

Articles

Mu H, Høy CE: The digestion of dietary triacylglycerols. *Progr Lipid Res* 2004; **43**: 105–133.

Alwaili K, Alrasadi K, Awan Z, Genest J: Approach to the diagnosis and management of lipoprotein disorders. *Curr Opin Endocrinol Diab Obes* 2009, **16**: 132–140.

Hegele RA: Plasma lipoproteins: genetic influences and clinical implications. *Nat Rev Genet* 2009; **10**: 109-121.

Hachem SB, Mooradian AD: Familial Dyslipidaemias: An Overview of Genetics, Pathophysiology and Management. *Drugs* 2006; **66**: 1949-1969.

Sniderman AD: Applying apoB to the diagnosis and therapy of the atherogenic dyslipoproteinemias: a clinical diagnostic algorithm. *Curr Opin Lipidol* 2004; **15**: 433–438.

Web sources

http://themedicalbiochemistrypage.org - the Medical Biochemistry Page