Physiologic importance of lipids

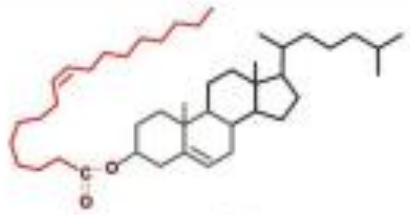
- **Lipids:**
  - Triacylglycerols (TAG)
  - Phospholipids (PL)
  - Free cholesterol (CH) and cholesteryl (CHE)
  - Free fatty acids (FFA)

- **Importace of lipids are**
  - (1) an important source of energy (TAG)--adipose tissue (TAG) form in lean humans about 1/5 of body weight represents the supply of ca. 570000 kJ, enough for about 3 months a complete starvation
  - (2) The starting material for the formation of a variety of substances (CH)
  -- signaling molecules (steroids, prostaglandins, enzymes, cofactors)
  -- components of cell membranes (esp. Phospholipids and CH)
  -- formation of bile acids

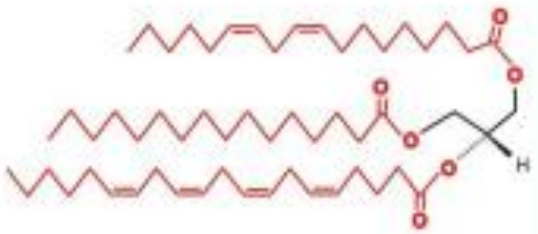
  Disorders: **hyperlipoproteinemia (HLP) / dyslipidemia**
  - group of metabolic diseases characterized by increasing lipid and lipoproteins in the plasma due to
  --their increased synthesis
  -- reduced catabolism of particles
  --respectively. reduction of particulate matter (esp. HDL)
  many **HLP** is atherogenic
  - but beware! increased levels of atherogenic lipoproteins in the plasma may not be at all in relation to the amount of subcutaneous fat, thus **HLP ≠ obesity!**

- **Lipoproteins (**concetration of lipoproteins in plasma is a result of the interaction of genetic factors with the external factors environment)

Important lipid classes

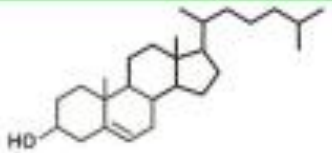


cholesteryl ester, CE

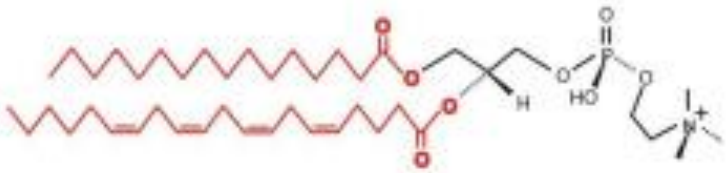


triacylglycerol, TAG (TG)

neutral = hydrophobic

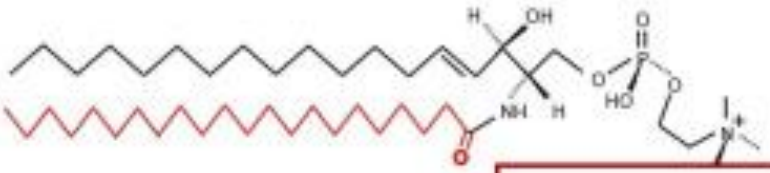


cholesterol, FC



phosphatidylcholine, PC

polar = amphiphilic



sphingomyeline,SPH

NEFA very polar

Digestion and absorption of lipids

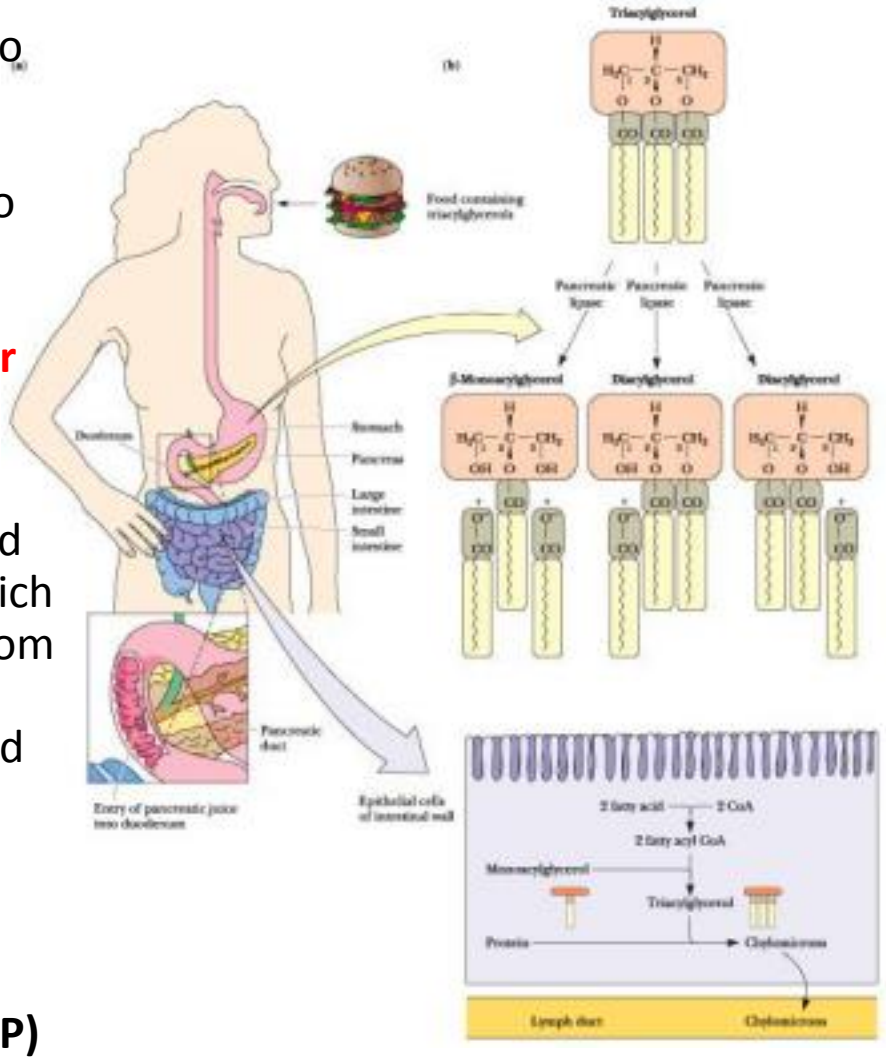
Water insoluble lipids contained in the diet (TAG, CH, phospholipids) are mechanically **emulsified by movements of the gastrointestinal tract and bile** so that they reach the enzymes necessary for their absorption

- TAG: intestine are digested by **pancreatic lipase** to free fatty acids and monoacylglycerol

- PL: digested by **pancreatic phospholipases**

- CH: cholesterol esters **Pancreatic cholesteryl ester hydrolase** to free CH

incomplete absorption (~ 30-60%)
together with bile acids, vitamins soluble in fats and other substances make up the. **mixed micelles**, which are either diffusion or incorporation and release from the membrane absorbed into **enterocytes** are undergoing re-re-esterification into TAG to resorbed lipids are added **apolipoproteins** and thus **chylomicrons** are formed they are released from enterocytes into lymph and then into the blood



In plasma circulating lipids as part **of lipoprotein (LP)**

Lipoproteins

lipoproteins = macromolecular complexes (particles) consisting of - a protein (= apolipoproteins and enzymes), structural integrity, binding to receptors, lipid exchange lipidů- (CH, CHE, TAG, PL), the outer layer - PL, CH, core - CHE TAG,

circulating lipoproteins:

- (1) resulting from intestine- chylomicrons, HDL;

- (2) formed in the liver: VLDL (very low density lipoproteins), IDL (intermediate density lipoproteins), LDL (low density lipoproteins), HDL (high density lipoproteins)

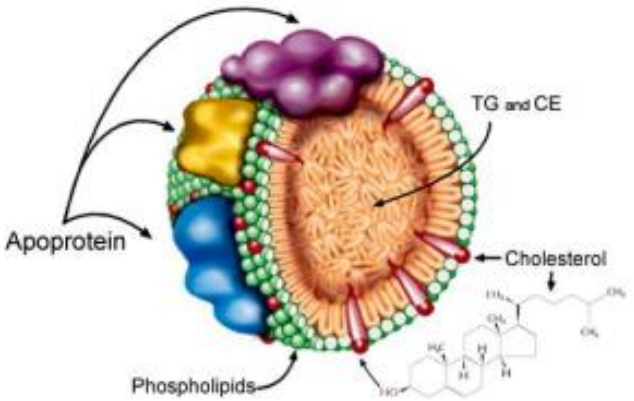
- (3) incurred in circulation: Lp (a) - the Circus. LDL and apo-a (liver)

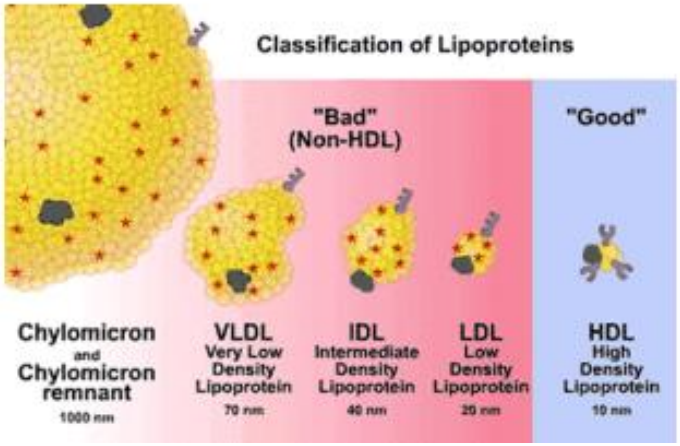
composition (lipids and apolipoproteins) differs between lipoproteins - VLDL and chylomicrons are rich in TAG (TAG >>>> CH)

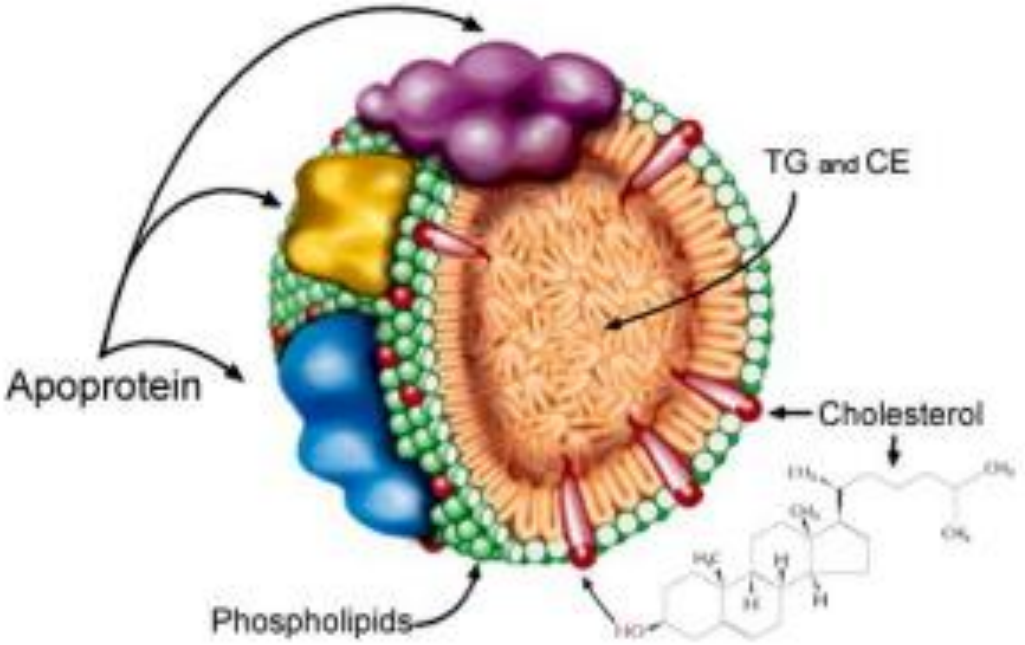
- LDL and HDL conversely CH >>>> TAG

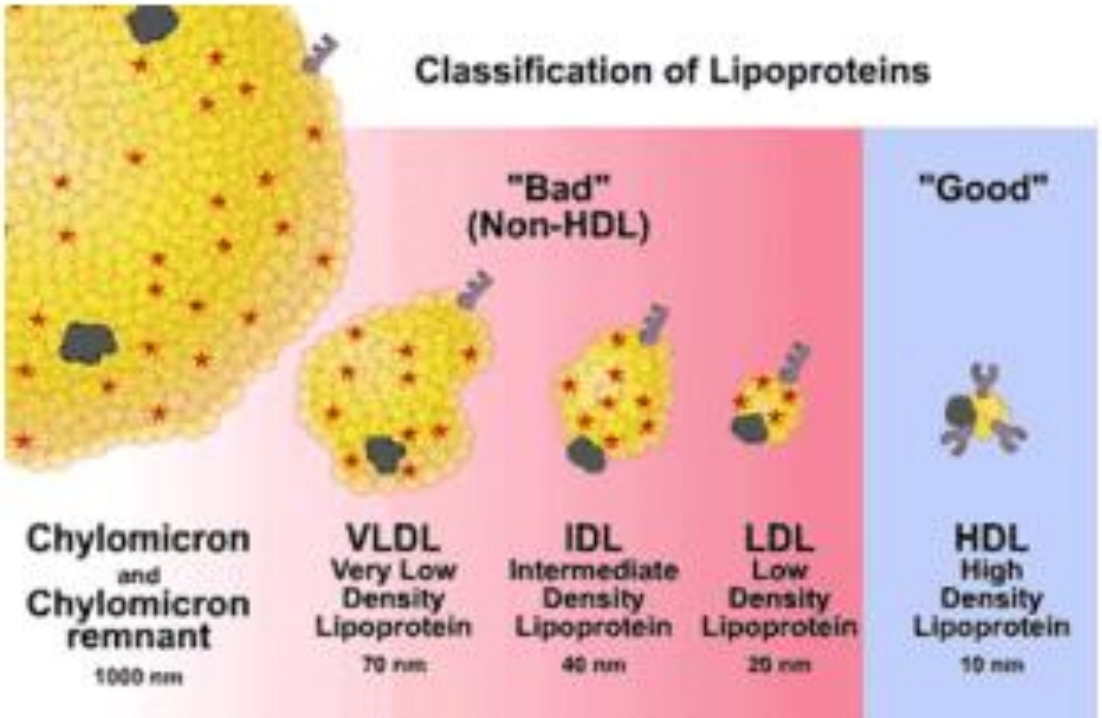
Different lipoproteins have a different metabolic fate

plasma normally contains: - <1% chylomicrons, - <10% VLDL - residue of LDL and HDL






TG and CE
Apoprotein
Cholesterol
Phospholipids


Classification of Lipoproteins
"Bad"
(Non-HDL)
"Good"
Chylomicron
and
Chylomicron
remnant
1000 nm
VLDL
Very Low
Density
Lipoprotein
70 nm
IDL
Intermediate
Density
Lipoprotein
40 nm
LDL
Low
Density
Lipoprotein
20 nm
HDL
High
Density
Lipoprotein
10 nm

Apolipoproteins

are part of the particles varies with its proportion and accordingly also the working of lipoproteins

- Participates in the structure of the particles and allow the transport of lipids in an aqueous medium

- Are enzyme cofactors of lipid metabolism

- Particle mediate binding to specific cellular receptors

- Participate in the exchange between lipid particles

all particles that contain **apoB (apoB-100, or apo B-48) are atherogenic** - apoB-100 - binding to the LDL receptor - apoB-48 - receptor binding chylomicrons "leftovers"

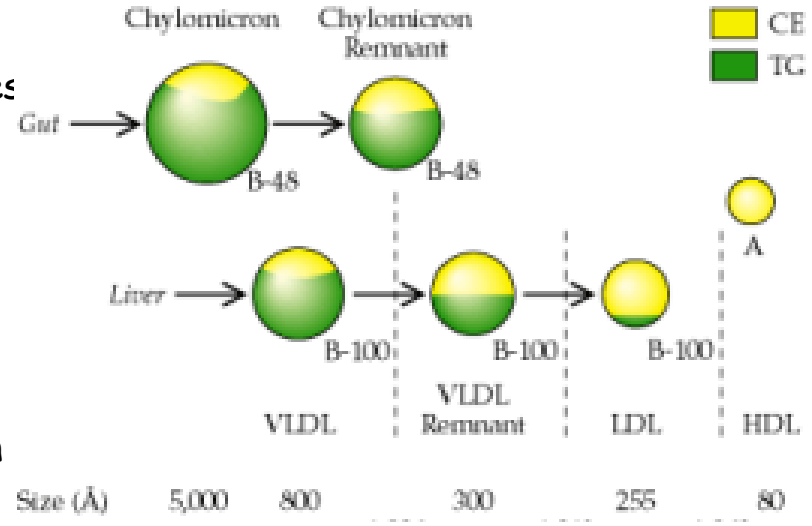
apoC are cofactors LPL (lipoprotein lipase) - apoC-II enables and apoC-III inhibits - and thus affect the rate of hydrolysis of TAG

apoE influences the uptake of lipoprotein or 'tails' livers

apoA contributes to the structure of HDL, LCAT cofactor and binding to HDL receptor-reduced levels of apoA are atherogenic

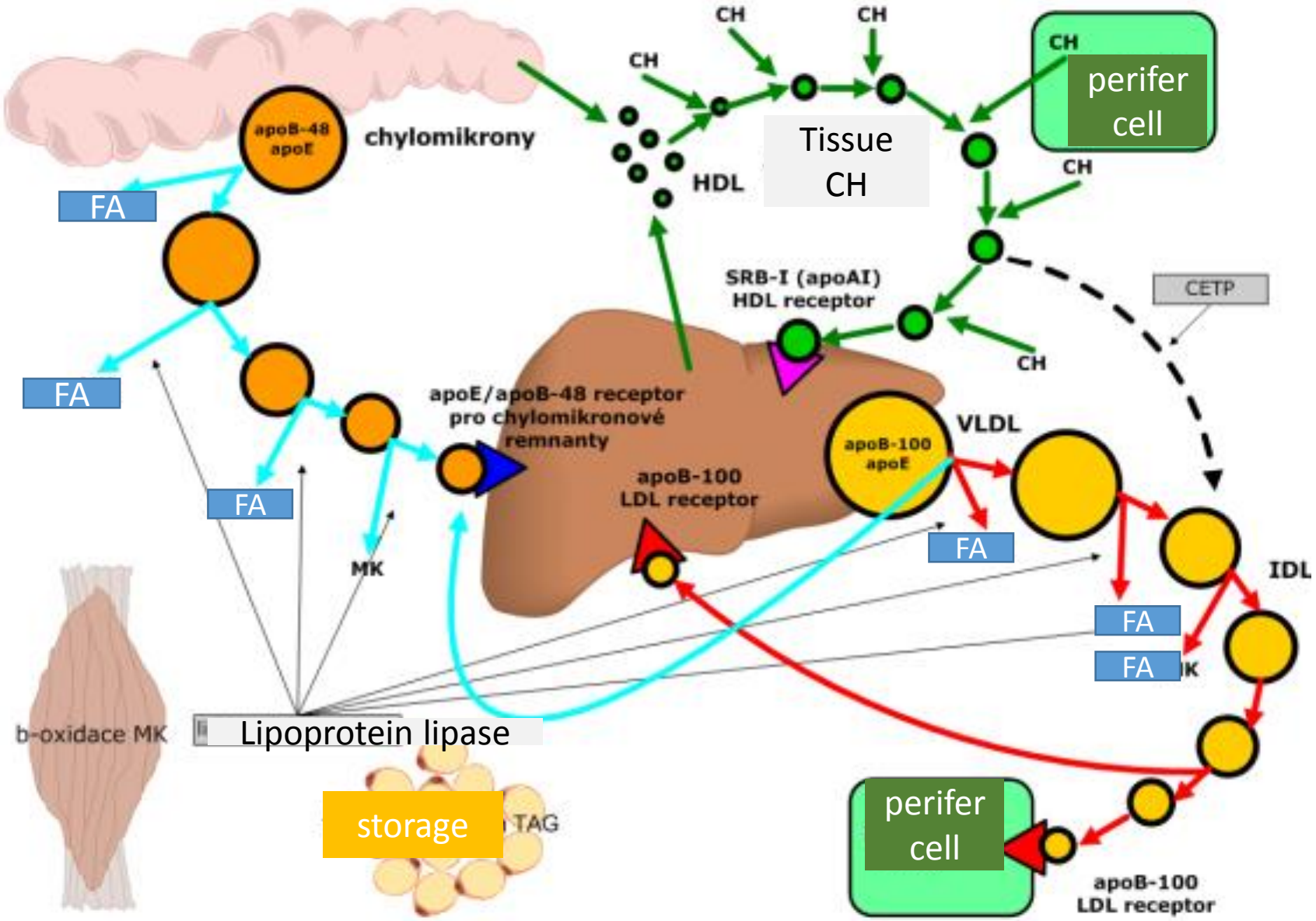
apo (a) with their considerable homology with plasminogen acts as a competitive inhibitor of plasminogen (an enzyme dissolving fibrin, i.e. blood clot), however, without its catalytic activity, and an increased risk of **thrombosis**

Částice	apoP
Chilom.	**apoB-48**, A, C, E
VLDL	**apoB-100**, C, E
LDL	**apoB-100**
HDL	**apoA**, C, D, E
Lp(a)	apo(a), **apoB-100**



Lipid transport

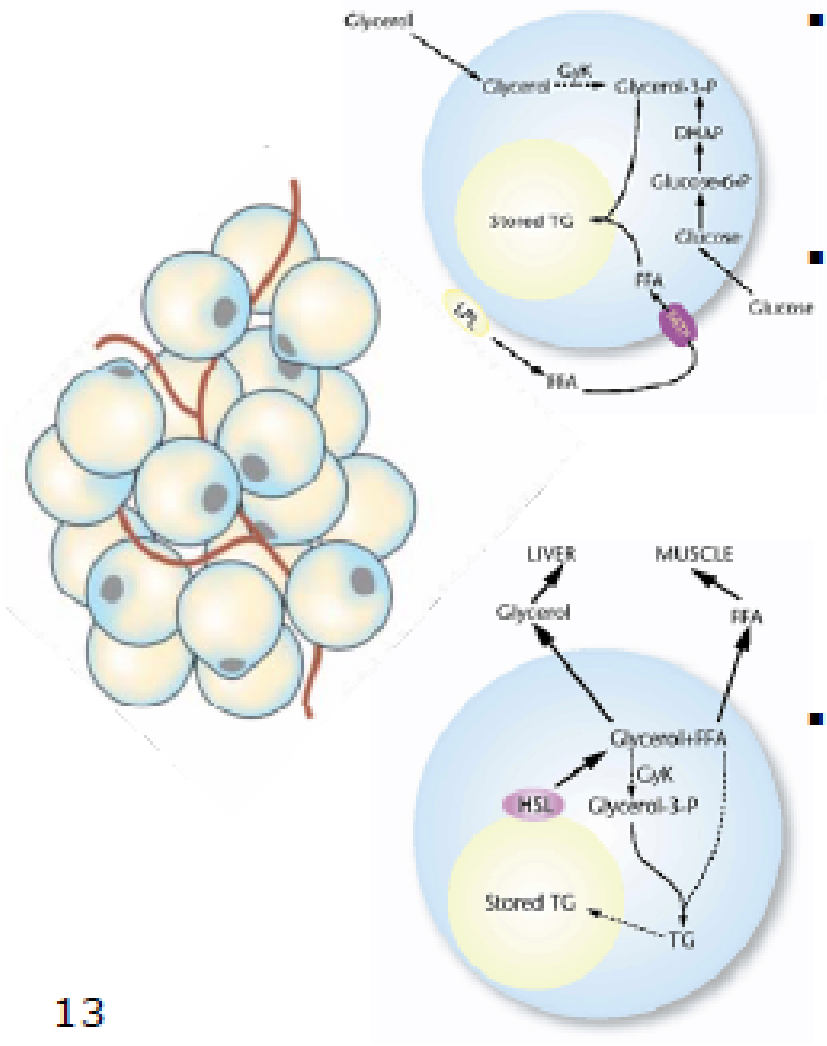
- postprandial phase – digestion of lipids from the diet
- fasting state – delivery of lipids to the tissues in need


CH
CH
CH
CH
CH
perifer cell
apoB-48 apoE
chylomikrony
HDL
Tissue CH
FA
FA
FA
SRB-I (apoAI) HDL receptor
CETP
CH
apoE/apoB-48 receptor pro chylomikronové remnanty
apoB-100 LDL receptor
apoB-100 apoE
VLDL
FA
IDL
FA
FA
MK
b-oxidace MK
Lipoprotein lipase
storage
TAG
perifer cell
apoB-100 LDL receptor

TAG transport

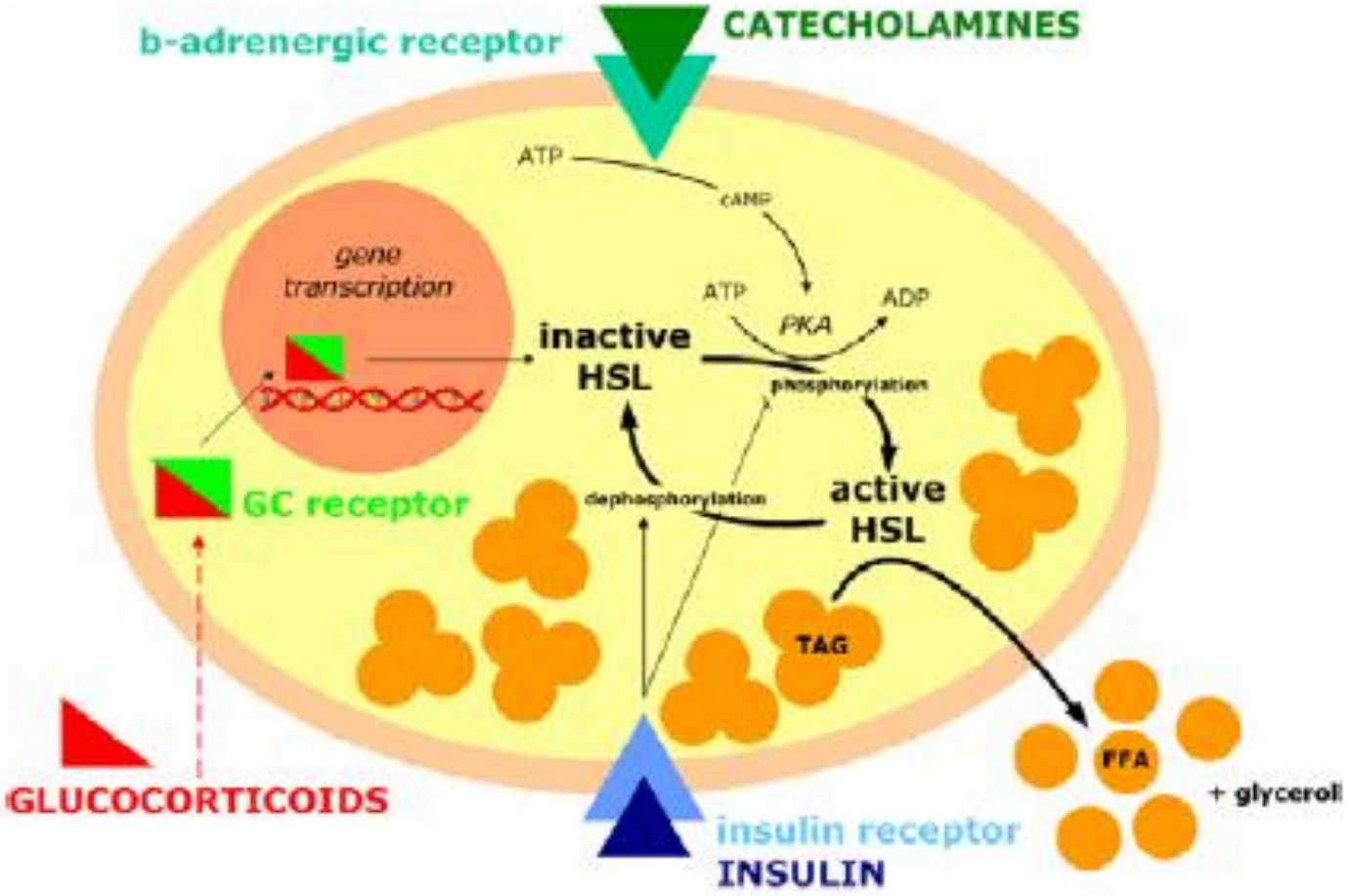
- **chylomikrone** formed in enterocytes provide TAG for muscle (=**energy substrate**) and adipose tissues (= storage)
- **FFA** are released from lipoprotein's TAG; – by **LPL** (enzyme bound to endothelium of blood vessels esp. in adipose tissue, muscles, myocardium),
  – by **hepatic lipase** in hepatocytes
- FFA are utilised by either **β-oxidation** to provide immediate energy (glycerol is used for gluconeogenesis in liver) or for **re-synthesis of TAG** for storage
- storage TAG **(adipose tissue)** can provide FFA upon hydrolysis by **hormone-sensitive lipase** (HSL)
- above mentioned processes are regulated by **hormones:** – **inzulin** activates LPL and inhibits HSL, – **catecholamines** and **glucocorticoids** activate HSL
- chylomicrons deprived of dietary TAG form **chylomikron remnants** carrying remaining dietary cholesterol; remnants are taken up by liver, – binding to the receptor for chylomicron remnants via **apoB-48**
- liver form **VLDLs** from:– (1) TAG synthesized de novo from acetyl-Co A from surplus of saccharides (after replenishing the liver glycogen), – (2) remaining dietary TAG s CH, – (3) remaining circulating FFA, – (4) de novo synthesized CH
- VLDLs circulate and are - similarly to chylomicrons - source of TAG for peripheral tissues (LPL), gradually transforming into IDL and LDL

Regulation of the balance between lipid storage and mobilization in adipocytes



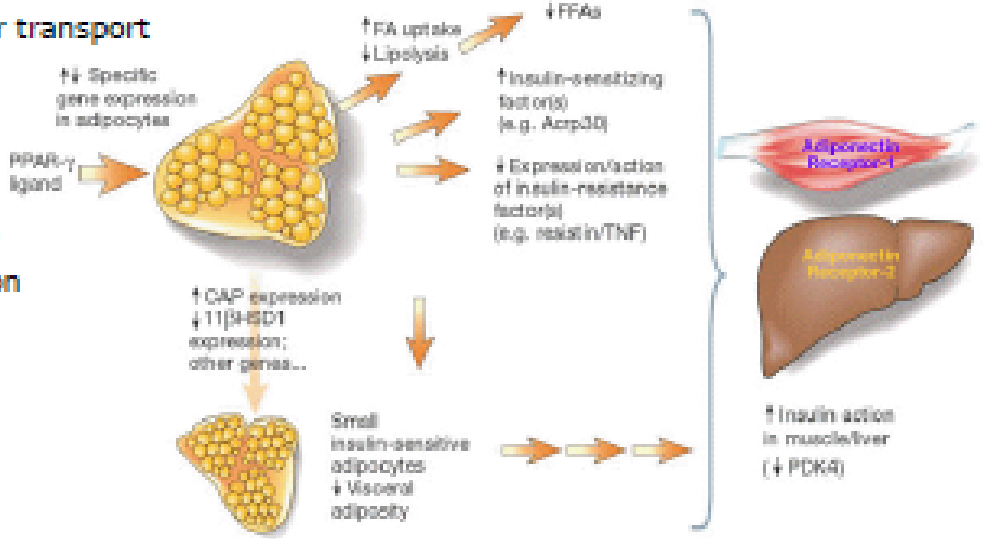
- the balance (ratio between **lipogenesis** and **lipolysis**) is a product of continuous neurohumoral regulation reflecting feeding/fasting cycling and immediate energy requirements of the body
- (a) normal adipocytes in a fed (postprandial) state
  - glucose is taken up by adipocytes via GLUT4 stimulated by **insulin**
  - FFA are released from TAG rich lipoproteins (mainly chylomicrons) by the action of LPL stimulated by **insulin**
  - surplus of glucose is the main source for TAG production
- (b) normal adipocytes in a fasted state
  - the stored TAG undergoes lipolysis mediated by HSL into glycerol and FFA, the latter are released for utilization in liver and muscle
  - activity of HSL is stimulated by catabolic hormones (**glucocorticoids**, **catecholamines**, ...)

Hormone-sensitive lipase (HSL)

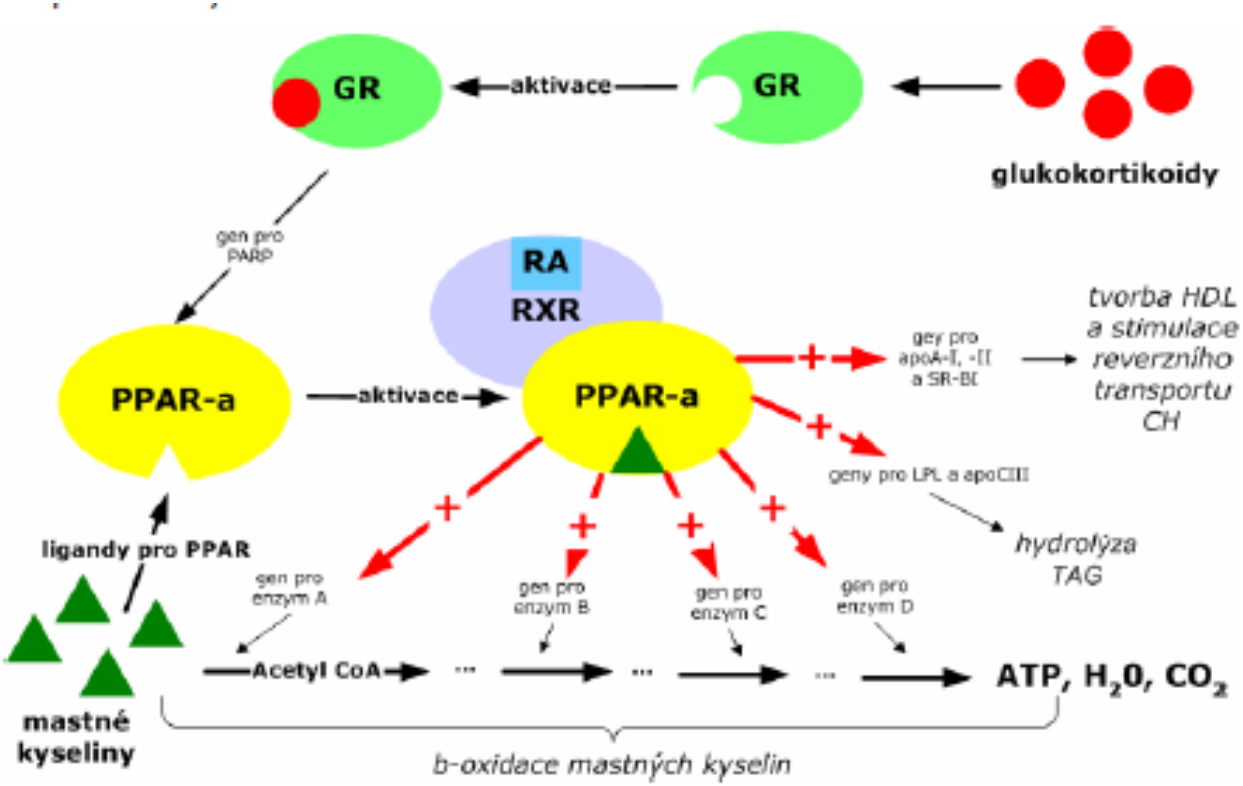


Transcriptional regulation of genes involved in TAG metabolism

- regulation by transcription factors from the family of nuclear receptors
- **(1) PPARs** (peroxisome proliferator activator receptors)
  - family of nuclear receptors PPARs (PPARα, γ and δ) regulating gene transcription of certain genes under the activation by lipophilic ligands
    - e.g. dietary polyunsaturated fatty acids or prostaglandin derivatives
  - PPAR/RXR heterodimers likely function as a cellular „**lipostat**"
    - PPARα act mainly in liver – activation of FA catabolism (↑ β-oxidation)
    - PPARγ act mainly in adipose tissue – stimulation of lipogenesis and adipocyte differenciation
    - PPARδ expressed ubiquitously – involved in the regulation of thermogenesis
- **(2) LXR** (liver X receptor)
  - ↑ expression of ATP-binding cassette transporter A1
- **(3) FXR** (farnesol X receptor)
  - regulates bile acid synthesis and their transport
- **(č) RXR** (retinoid X receptor)
  - binds retinoic acid
  - heterodimerises with all above mentioned receptors
  - heterodimers (= transcription factors) bind to responsive elements in promotor sequences of numerous genes and modulate their transcription
- **pharmacologic activation**
  - **fibrates** - PPARα agonists = hypolipidemic drugs
  - **glitazons** - PPARγ agonists = anti-diabetic drugs



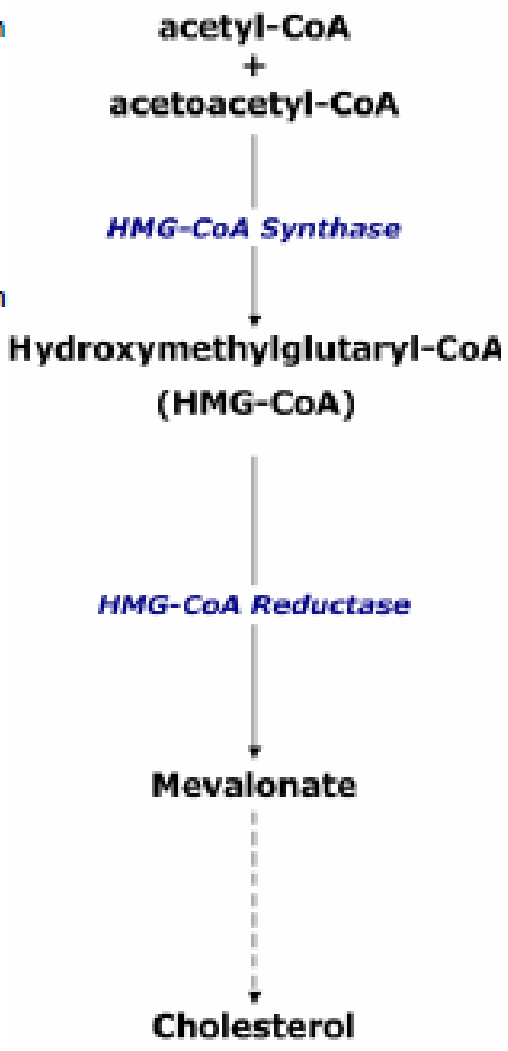
- *PPARα regulated genes:*
- *- Activation of fatty acid oxidation*
- *- Reduction of plasma TAG levels*
- *- Reduction of plasma level of CH*



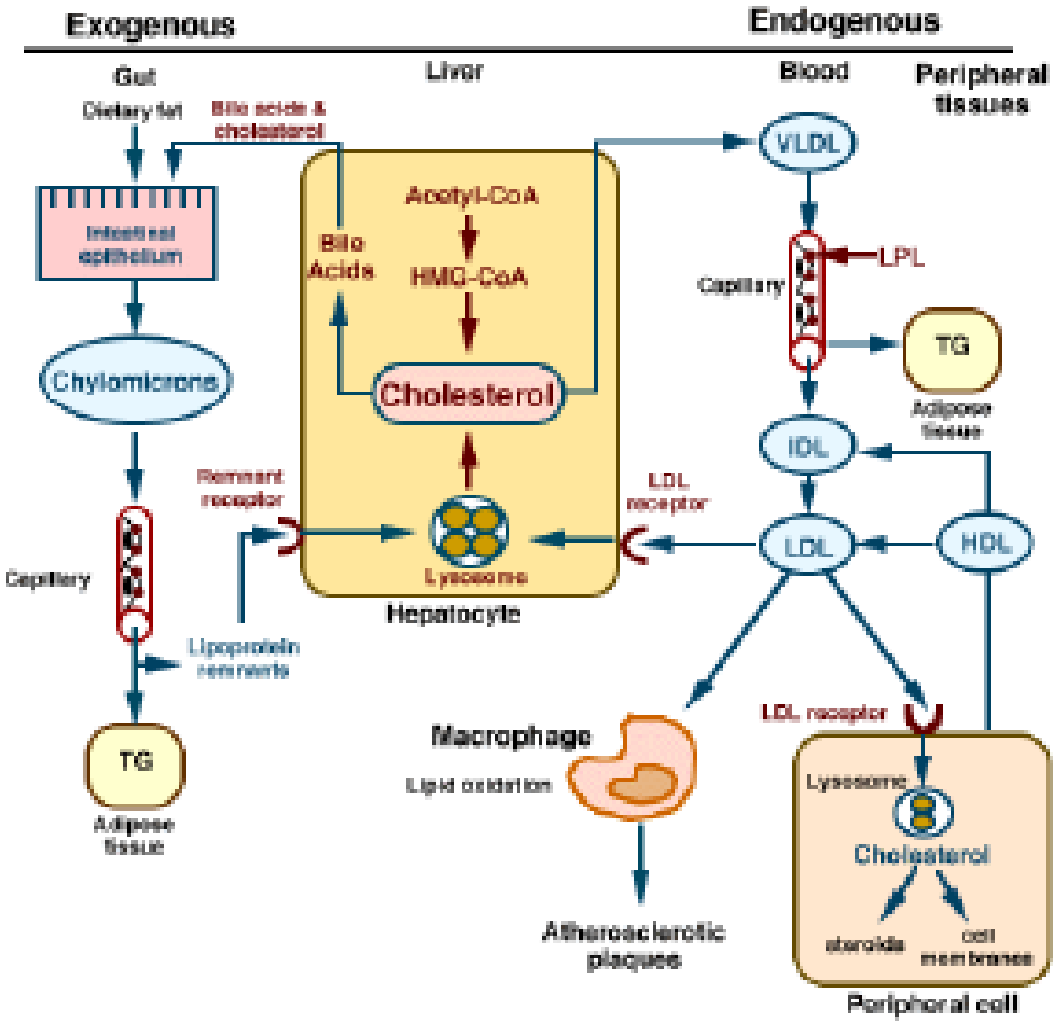
Cholesterol (CH)

CH transport – to the periphery

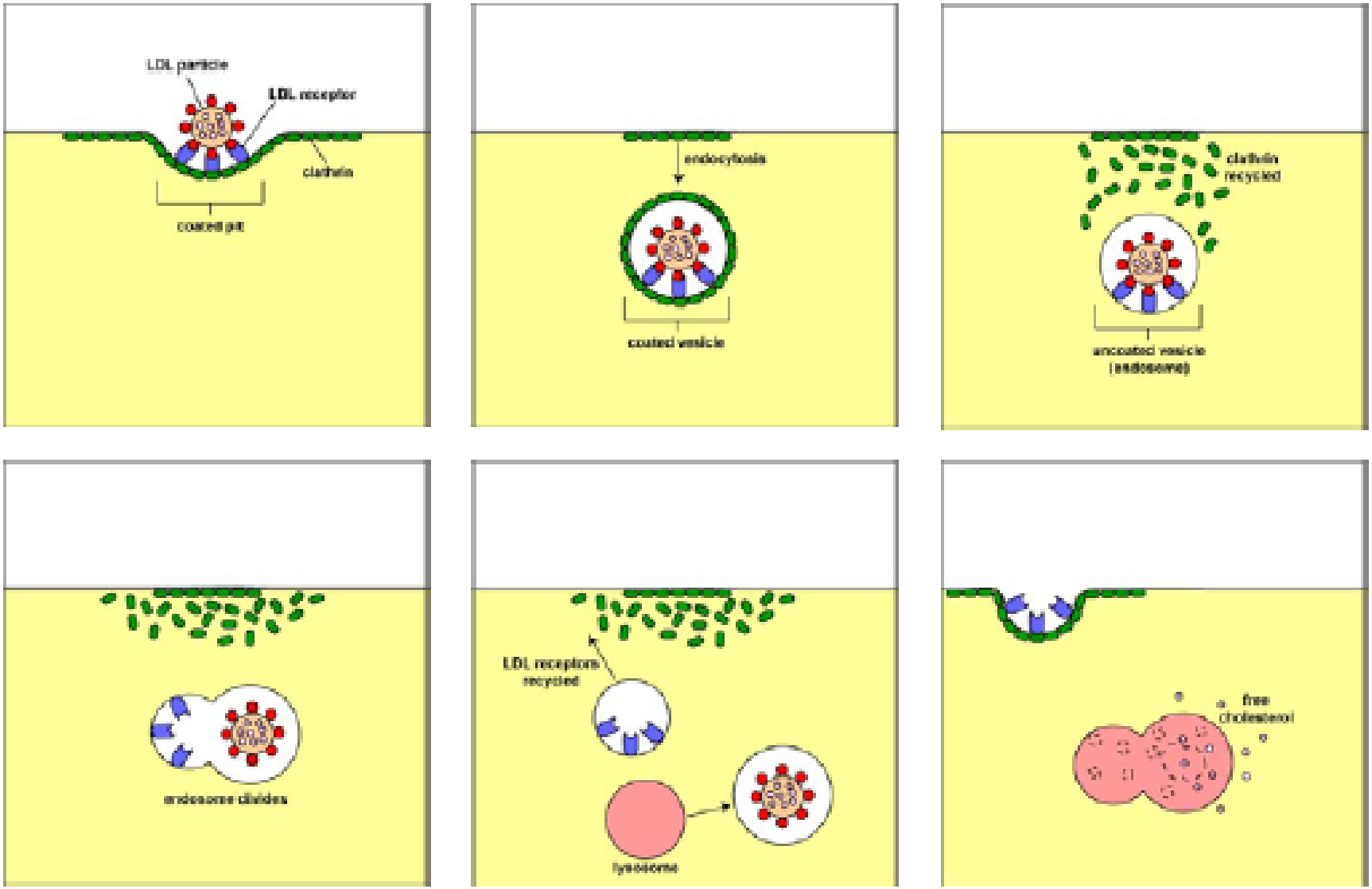
- CH is transported by lipoproteins more or less independently on TAG
- CH is an indispensable for all cells (for plasma membranes, steroid hormones and vit. D) therefore body can – in case dietary intake is not sufficient – **synthesize CH endogenously** (every cell but most significantly in the liver)
  - endogenous CH production should be (but not always is!) balanced to its exogenous intake
- CH leaves the body in the form of bile acids and CH dissolved in the bile
- sources of CH
  - (1) diet
  - (2) endogenous (from acetyl-CoA)
  - (3) re-absorbed from bile (enterohepatal circulation)
- CH is carried by
  - chylomicrons = dietary
  - VLDL, IDL, LDL = endogenous synthesis in the liver
  - HDL = reverse transport from tissues to the liver
- LDL particles are formed from VLDL after removal of TAG and are thus rich for CH – source of CH for peripheral tissues (most of the CH is taken by liver, adrenal gland, CNS a adipose tissue)
  - **(1) LDL-receptor dependent uptake**
    - binding to LDL-receptor (apoB-100/apoE recognition site of LDL receptor), internalisation and release of free CH
  - **(2) non-LDL-receptor dependent** (scavenger) **uptake**
    - monocytes/macrophages via "scavenger" receptors – uptake of oxidised or glycated LDL particles → **atherosclerosis**



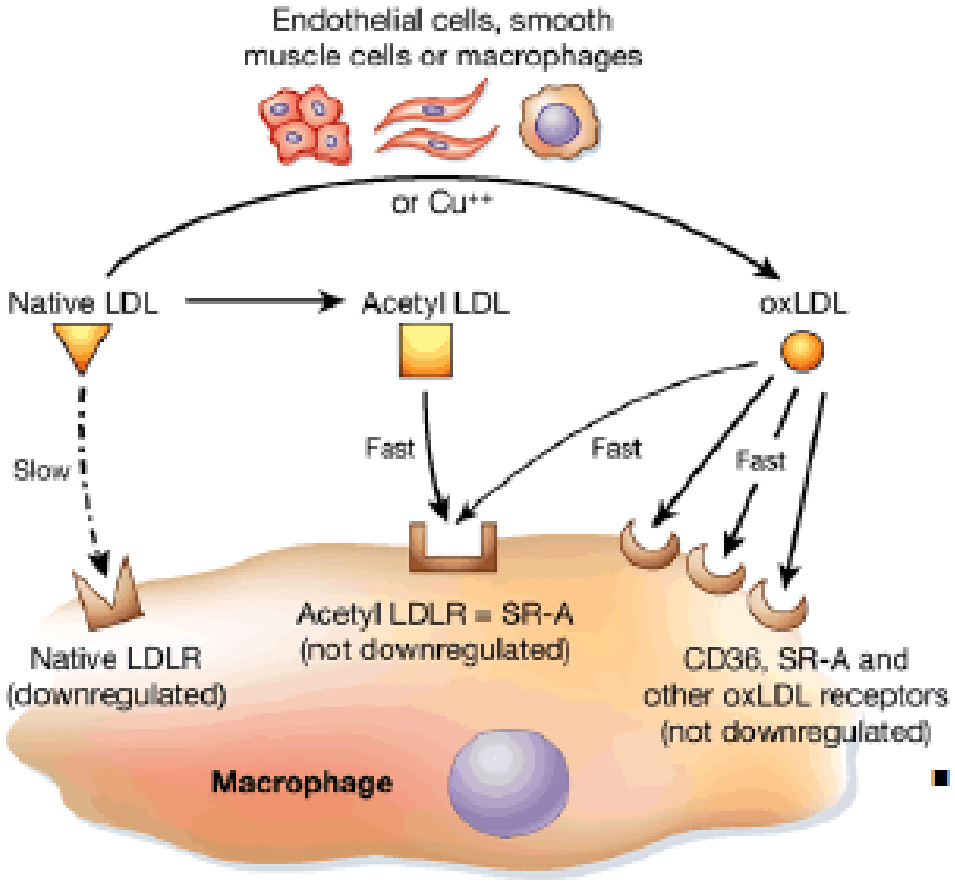
Overview of CH metabolism



LDL receptor endocytosis



Non-LDLR-dependent CH uptake



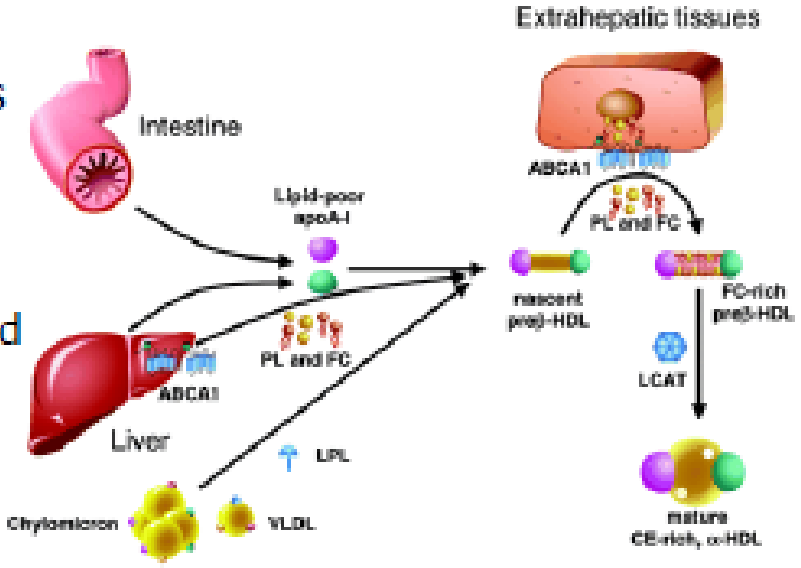
- LDLs are involved in the atherogenesis
  - "foam" cell formation = CH from LDLs taken by monocytes/macrophages in the vascular wall
    - however, incubation of monocytes/macrophages or vascular smooth muscle cells with even quite high concentrations of LDL does not induce them to take up CH (LDLRs down-regulate) → **LDL must be chemically modified to become atherogenic** (in vivo by oxidation → oxLDLs)
    - the highest atherogenic potential is associated with "small dense LDLs" (oxidised and TG rich)
- mediated by scavenger receptors different from the LDLR
  - scavenger receptor type A (SR-A)
  - other members of CD36 family

Regulation of CH synthesis

- CH biosynthesis is extremely complex, however, **HMG-CoA Reductase** is the rate-determining step on the pathway for synthesis of cholesterol and a major control point
- **(A) long-term regulation of cholesterol synthesis**
  - (1) regulated formation of HMG-CoA Reductase and other enzymes of the pathway for synthesis of cholesterol
    - regulated transcription: a family of transcription factors designated **SREBP** (Sterol Regulatory Element Binding Proteins) regulate synthesis of cholesterol and fatty acids
      - SREBP-2 mainly regulates cholesterol synthesis
      - SREBP-1 mainly regulates fatty acid synthesis
    - when sterol levels are low, SREBP-2 is released by cleavage of a membrane-bound precursor protein, SREBP-2 activates transcription of genes for HMG-CoA Reductase and other enzymes of the pathway for cholesterol synthesis → activated SREBPs enter the nucleus and turn on the expression of genes that contain **sterol regulatory element** (SRE) elements in their promoters, such as the low-density lipoprotein receptor (LDLR), HMG-CoA synthase, squalene synthase and fatty acid synthase
  - (2) regulated degradation (proteolysis) of HMG-CoA Reductase
    - proteolysis of HMG-CoA Reductase is stimulated by CH, by oxidized derivatives of CH, by mevalonate, and by farnesol
      - HMG-CoA Reductase includes a transmembrane sterol-sensing domain that has a role in activating degradation of the enzyme via the proteasome
- **(B) short-term regulation**
  - HMG-CoA Reductase is inhibited by phosphorylation, catalyzed by **AMP-Dependent Protein Kinase** (which also regulates FA synthesis and catabolism)
    - this kinase is active when cellular AMP is high, corresponding to when ATP is low → thus, when cellular ATP is low, energy is not expended in synthesizing cholesterol
- **(C) pharmacological**
  - hypolipidemis drugs - competitive inhibitors of HMG-CoA Reductase (statins)

Reversed CH transport (RCT)

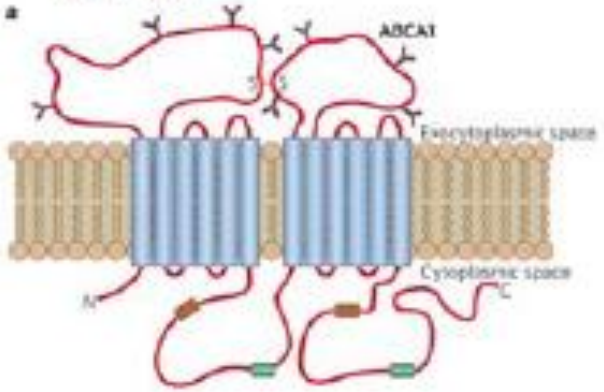
- RCT is mediated by **HDLs formed in liver** and enterocytes
- (1) secretion & lipid acquisition
  - begins with the secretion of lipid-poor apoA-I by liver and intestine followed by acquisition of CH and PL via ABCA1-mediated efflux from the liver
    - **apoA-I** gene expression is regulated by many factors: dietary fat, alcohol, estrogens, androgens, thyroid hormones, retinoids, glucocorticoids, …

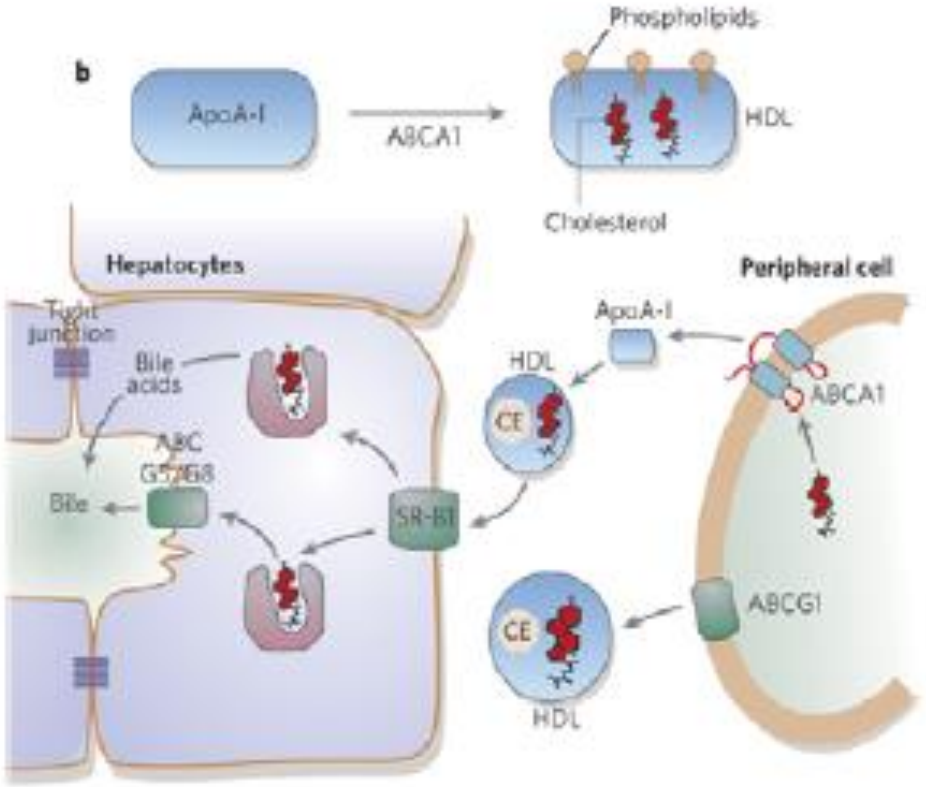


  - transfer of CH, PL, and apolipoproteins from chylomicrons and VLDL during LPL-mediated lipolysis to form **"nascent" pre-ß HDL** particles
  - lipid-poor apoA-I and pre-ß HDL particles acquire additional CH and PL from cells in extrahepatic tissues progressively generating particles that are more cholesterol enriched
    - (1) by passive diffusion – bidirectional
    - (2) by scavenger receptor type B-I (SR-BI) – bidirectional
    - (3) by transporter-facilitated process - ATP-binding cassette transporter A1 (**ABCA1**) – unidirectional

ATP-binding cassette transporter A1

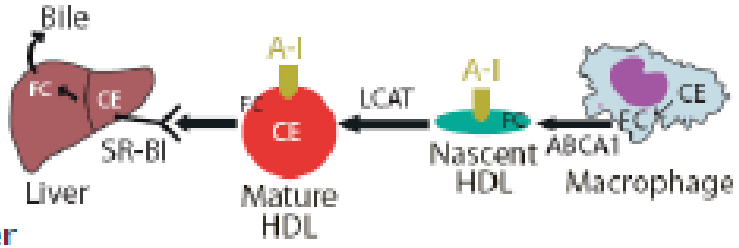
- ABCA1 is a multiple membrane-spanning protein with two nucleotide-binding folds linked by a cytoplasmic peptide sequence
  - mutations in ABCA1 gene lead to **Tangier disease** (↓↓ HDL → atherosclerosis)
- ABCA1 promotes the transfer of CH to lipid-poor forms of ApoA-I HDLs (mechanisms is not fully understood), but ABCA1 apparently functions by translocating CH across the plasma membrane bilayer and presenting them to ApoA-I, which binds to ABCA1





RCT - continued

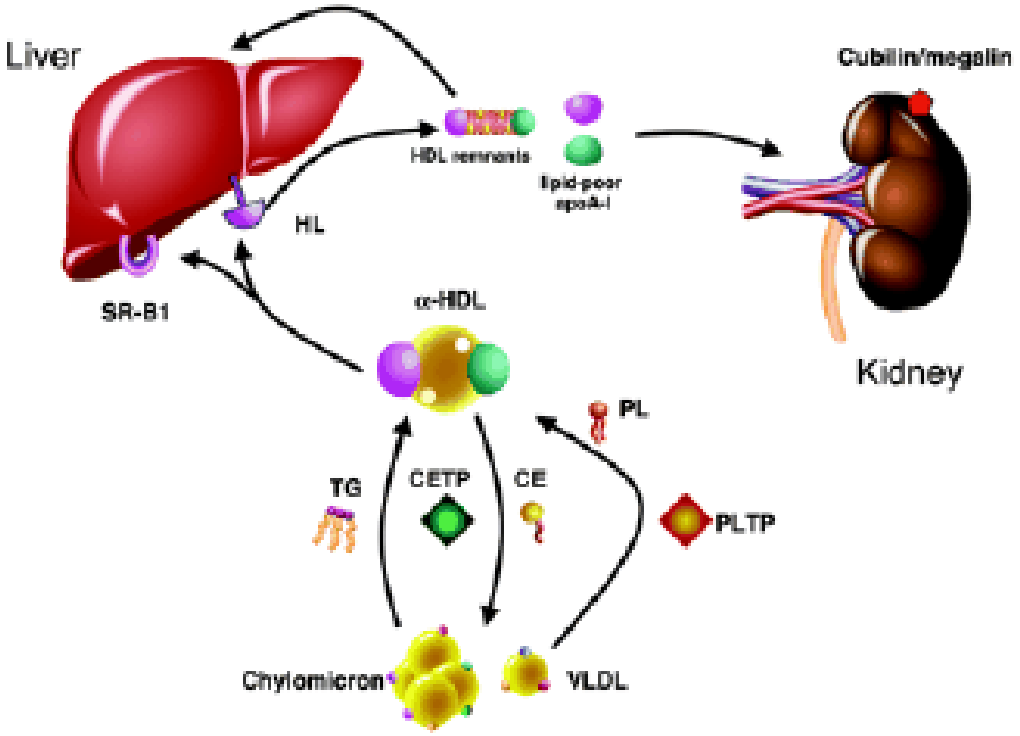
- (2) maturation of HDL particles
  - the enzyme **LCAT** [lecitin:cholesterol-acyltransferase], carried on HDL particles activated by apo-proteins of HDLs, esterifies the free CH to CHE, which migrate to the core of the HDL particle to form mature HDL particles which can further acquire additional lipid from certain cells via efflux mediated by ABCG1 and SR-BI intravascular



- (3) intravascular modelling of HDL by lipases and lipid transfer factors
  - an important determinant of the rate of HDL clearance from the circulation
  - enzyme **CETP** [cholesterol ester transfer protein]
    - catalyses reverse process - heteroexchange of CHE between HDLs and TAG-rich lipoproteins (chylomicrons and VLDLs) which results in CHE depletion and TG enrichment of HDL
  - hepatic lipase
    - modification of TG-rich HDL releases lipid-poor apoA-I and HDL remnant particles
    - lipid-poor apoA-I is filtered by the renal glomerulus and then degraded by proximal tubular cell receptors such as cubilin/megalin system
    - HDL remnants may bind to putative receptors in liver that mediate HDL holoparticle uptake, internalization, and degradation
  - HDL contain **paraoxonase** – an enzyme protecting CH (in HDL and LDL) from oxidation and thus increase in its atherogenic potential
- (4) HDLs and their CH are removed from circulation in liver, kidney and steroidogenic tissues by two processes:
  - (1) selective CH uptake (liver mainly)
    - HDL bind HDL-receptor SR-BI via apoA-I, CH liberated and secreted by bile (either as a free CH or metabolised to bile acides)
  - (2) endocytic uptake of whole HDL particles (kidney)
    - HDLs filtered, reabsorbed in prox. tubule (megalin/cubilin system)

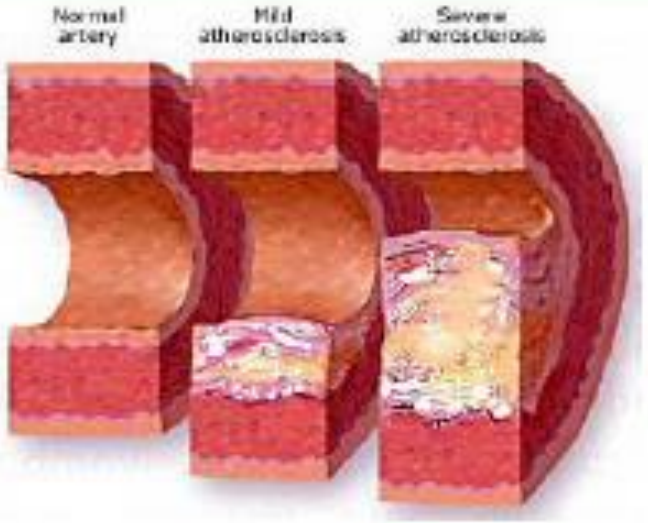
Summary of RCT

- in summary, efficiency of RCT is determined by:
  - (1) the rate of production of apoAI
  - (2) the rate of clearance of HDLs from circulation by liver (via SR-BI)
  - (3) the rate of CH esterification (↑ LCAT/↓ CETP)
  - (4) action of lipases (hepatic, lipoprotein) – variable TG content influence the rate of clearance of HDL



Hyper-/dyslipoproteinemia

- **hypercholesterolemia**
  - ↑ total CH, LDL (and all apoB particles)
  - ↓ HDL (apoA particles)
  - **risk factor of atherosclerosis**
    - identified and confirmed by numerous epidemiological studies

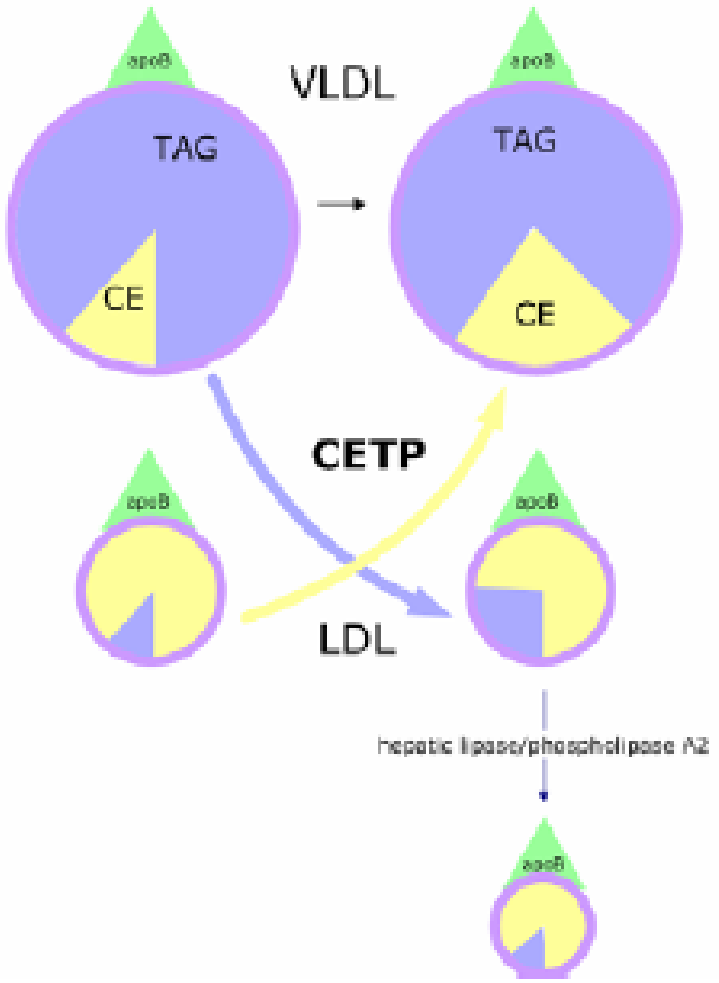


- **hypertriglyceridemia**
  - (1) ↑ isolated TAG (i.e. TAG-rich particles)
    - solely high TAG is not atherogenic (e.g. LPL deficiency)
  - **risk of acute pancreatitis ()**
    - TAG > 20-30 mmol/l
  - (2) ↑ TAG (i.e. TAG-rich particles) + FFA
  - **insulin resistance**
  - (3) ↑ TAG + ↑ apoB particles (due to high influx of FFA into liver) + ↓ HDL
  - **risk factor of atherosclerosis**

Atherogenic particles – LDL

- LDL, and especially **small dense LDL**, are the most atherogenic particles
  - small dense LDL more easily penetrate endothelium, they have lower affinity to LDL-R and get more easily oxidised and thus scavenged by macrophages in the vessel wall
  - CH prevails LDL and in chylomicron remnants, the latter is however quickly removed by liver (if not, these become extremely atherogenic)
  - LDL stays in plasma 9× longer than VLDL (so there is 9× more LDL than VLDL and since ~70% of all CH is carried by LDL this is a major determinant of its plasma concentration)
  - the risk of atherosclerosis rises with LDL concentrations, however, for any given LDL level the risk is determined by HDL levels!!!
    - low HDL levels increase the risk of atherosclerosis even when total CH and LDL are within reference interval
- atherogenic lipid profile:
  - ↑LDL (esp. small, dense, oxidised)
  - ↑apoB (= reflect better LDL particle number than conc. of LDL)
  - ↓HDL
  - ↑apo(a)
  - ↑TAG (if accompanied by ↑FFA)
    - TAG contribute to the formation of small dense LDL

Formation of small dense LDL particles



HLP classification

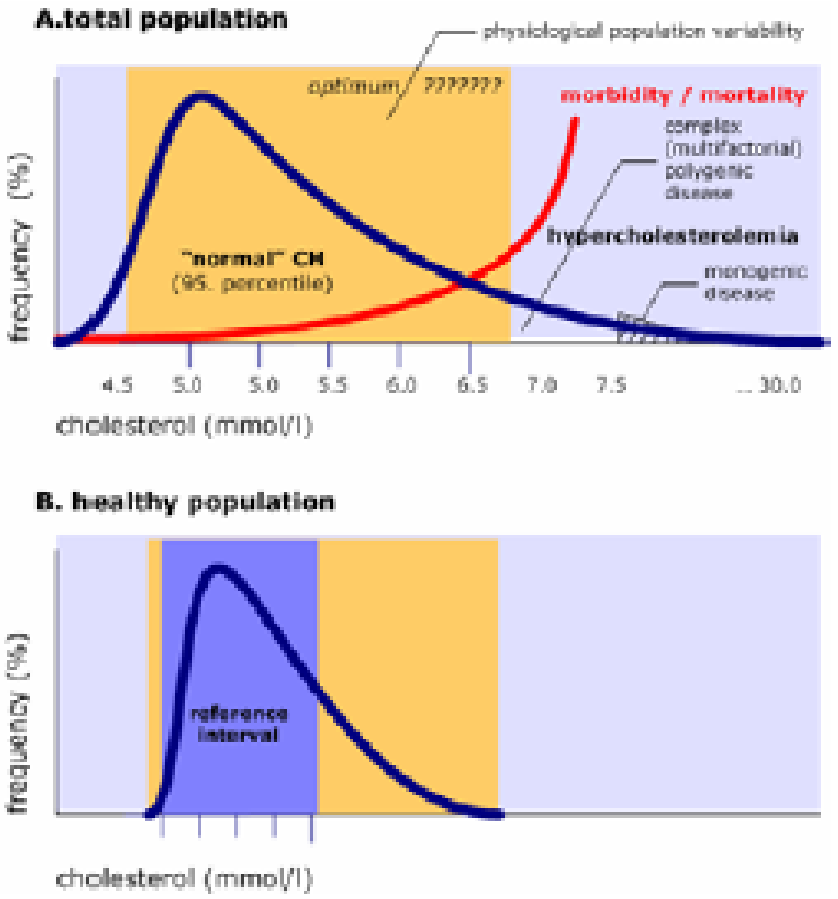
- several classification schemes available according to different criteria
  - electrophoretic mobility
  - clinical impact
  - ethiopathogenesis
- in the past – **Fredrickson classification** (phenotypes I - V)
  - lipoprotein mobility spectrum after electrophoretic separation
  - did not considered HDL!!!
- today – simple, therapeutically relevant clinical classification of HLPs considering plasma levels of lipids despite the ethiopathogenesis:
  - a) hypercholesterolemia
  - b) hypertriglyceridemia
  - c) mixed disorders
- ethiopathogenic (patho-physiological) classification
  - primary HLPs
  - secondary HLPs

Type	Particle elevated	Serum CH	Serum TAG	%
I	chylom	Normal to ↑	↑↑↑↑	<1
IIa	LDL	↑↑	Normal	10
IIa	LDL and VLDL	↑↑	↑↑	40
III	IDL	↑↑	↑↑↑	<1
IV	VLDL	Normal to ↑	↑↑	45
V	VLDL and chylom	↑ or ↑↑	↑↑↑↑	5

parameter	range	interpretation
Total CH	<5.2 mmol/l	↑Atherosclerosis
HDL	>1.6 mmol/l	↓Atherosclerosis
LDL	<3.4 mmol/l	↑Atherosclerosis
TAG	<1.8 mmol/l	↑Atherosclerosis
apoAI	1.2 - 1.7 g/l	↓Atherosclerosis
apoB	0.58-1.38g/l	↑Atherosclerosis
Lp(a)	<0.3 g/l	↑ Atherosclerosis

Etiology of HLPs

- HLPs are heterogeneous group of metabolic diseases characterised by increased plasma lipoproteins
  - >95. population percentile + mortality effect
  - **dyslipoproteinemia** is a term often used since not only high but also low levels can be a risk (e.g. HDL)
- HLPs are caused by:
  - a) increased synthesis of apolipoproteins
  - b) defect of intravascular processing by enzymes (e.g. LPL deficit)
  - c) defect uptake by membrane receptors (e.g. LDL receptor)
  - d) decreased removal of lipoproteins
- etiology
  - **primary HLPs** – genetic (inherited)
  - **secondary** – consequence of other disease
- genetics (disease vs. disposition)
  - polygenic – complex diseases" ("thrifty" genotype)
    - genetic predisposition + environmental factors (diet!!!)
  - monogenic – single gene



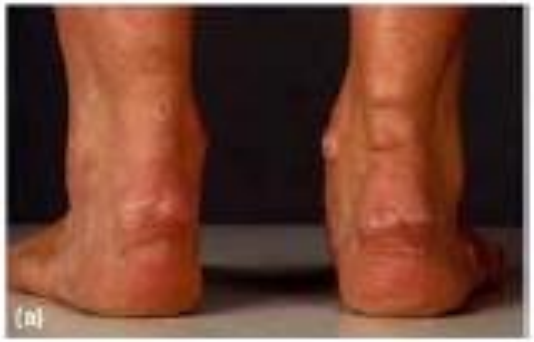
Primary HLPs

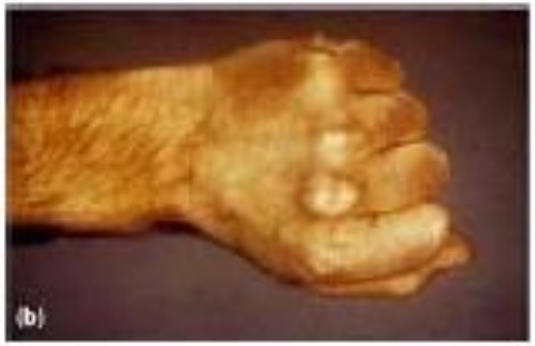
Disorder	Type (Fredrickson)	Cause
Familiar deficit of LPL	I	LPL gene mutations
Familiar deficit of apoC	I or V	apoC gene mutations
Fam. hypercholesterolemia	IIa	LDLR gene mutations
Familiar defective apoB-100	IIa	apoB gene mutations (defect of binding to LDLR – 10% of normal activity)
Polygenic hypercholesterolemia	IIa, IIb	Polygenic
Fam. combined hypelipidemia	IIa, IIb	Polygenic
Fam. dysbetalipoproteinemia	III	apoE gene mutations
Fam. hypertriglyreridemia		? (polygenic)

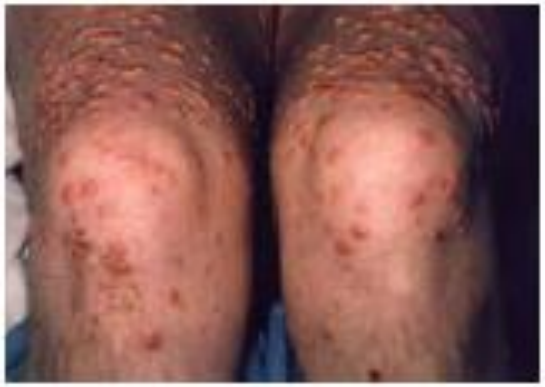
- monogenic diseases are very often **autosomal semidominant**, i.e. severity of the disease is graded according to the number of pathologic alleles
- all primary HLPs typically **do not respond to dietary interventions**, lipid lowering pharmacotherapy is necessary
- carriers are endangered by **premature cardiovascular disease** (esp. homozygous subjects with familiar

Familiar hypercholesterolemia (FH)

- the most common primary HLP
  - heterozygotes population prevalence 1:500
  - homozygotes 1:1 mil.
- FH is caused by **mutations in the LDLR gene** (chromosome 19)
  - >700 mutations identified
- **LDL receptor** (+part of plasma membranes = "coated pits")
  - periodic recycling (~1 × 10min) with ingestion of LDL particles
  - lysozomal enzymes release free CH and AA (from apolipoprotein apoB
- 5 functional classes of mutations:
  - 1) complete absence of the receptor (17 %)
  - 2) defective transport of receptor to the plasma membrane (54 %)
  - 3) defective binding of LDL
  - 4) defective internalisation of receptor + LDL complex
  - 5) defective liberation from endosome after internalisation and recycling to plasma membrane (22 %)
- increase of plasma CH depends on the type of mutation and hetero- or homozygosity (i.e. „**gene-dosage**" effect)
  - ~2× of normal [<5.2mmol/l] in heterozygotes
  - ~4-5× in homozygotes
- consequences of FH
  - multiple skin xantomas and tendon xantelasma, arcus corneae
  - **premature atherosclerosis**
    - mortality of MI in very young age in unrecognised homozygotes, before the 4th decade in heterozygotes
- **molecular genetic diagnostics** of suspicious cases and family members, follow-up, genetic counselling, agressive hypolipidemic therapy!!!!



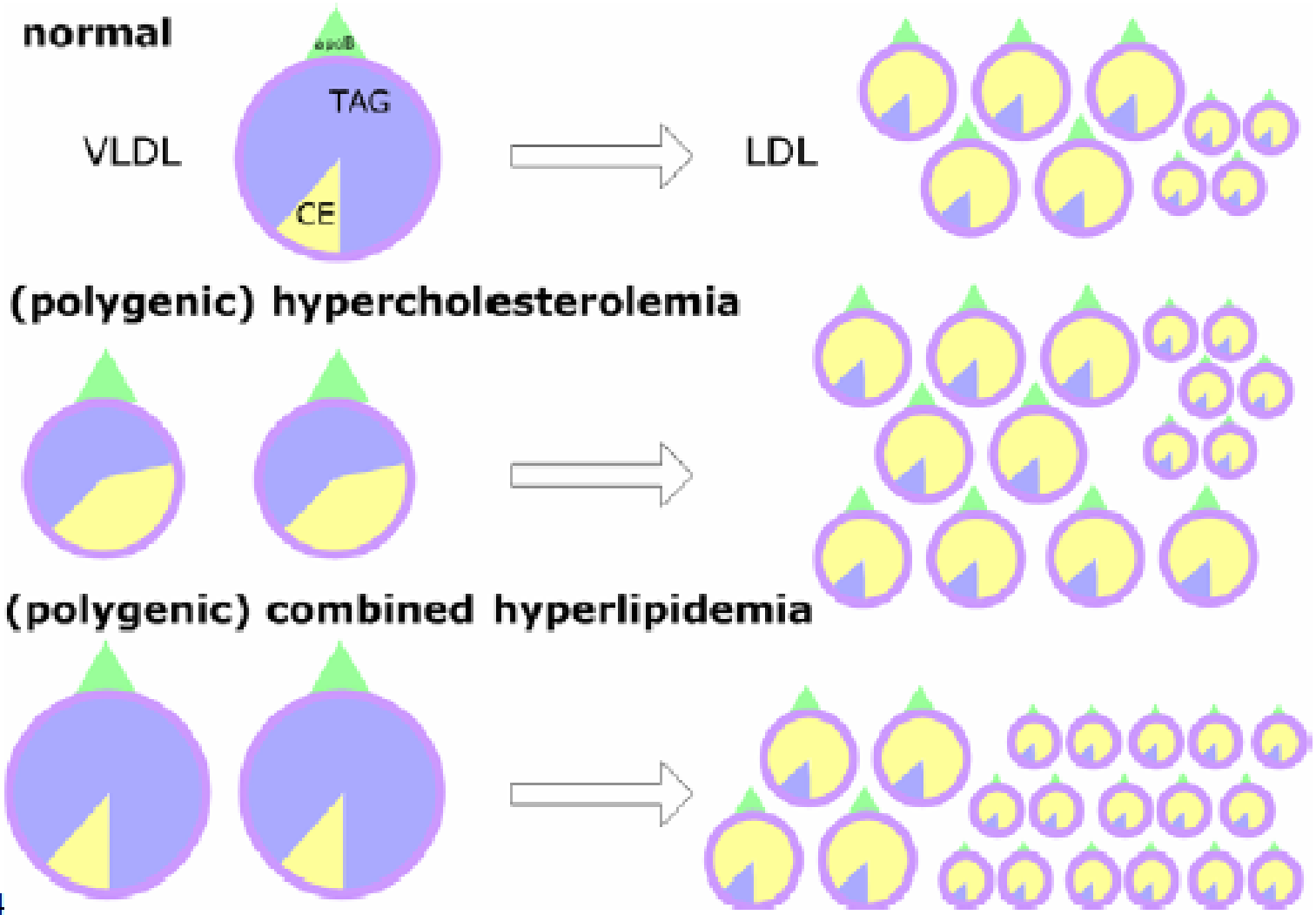




Polygenic HLPs

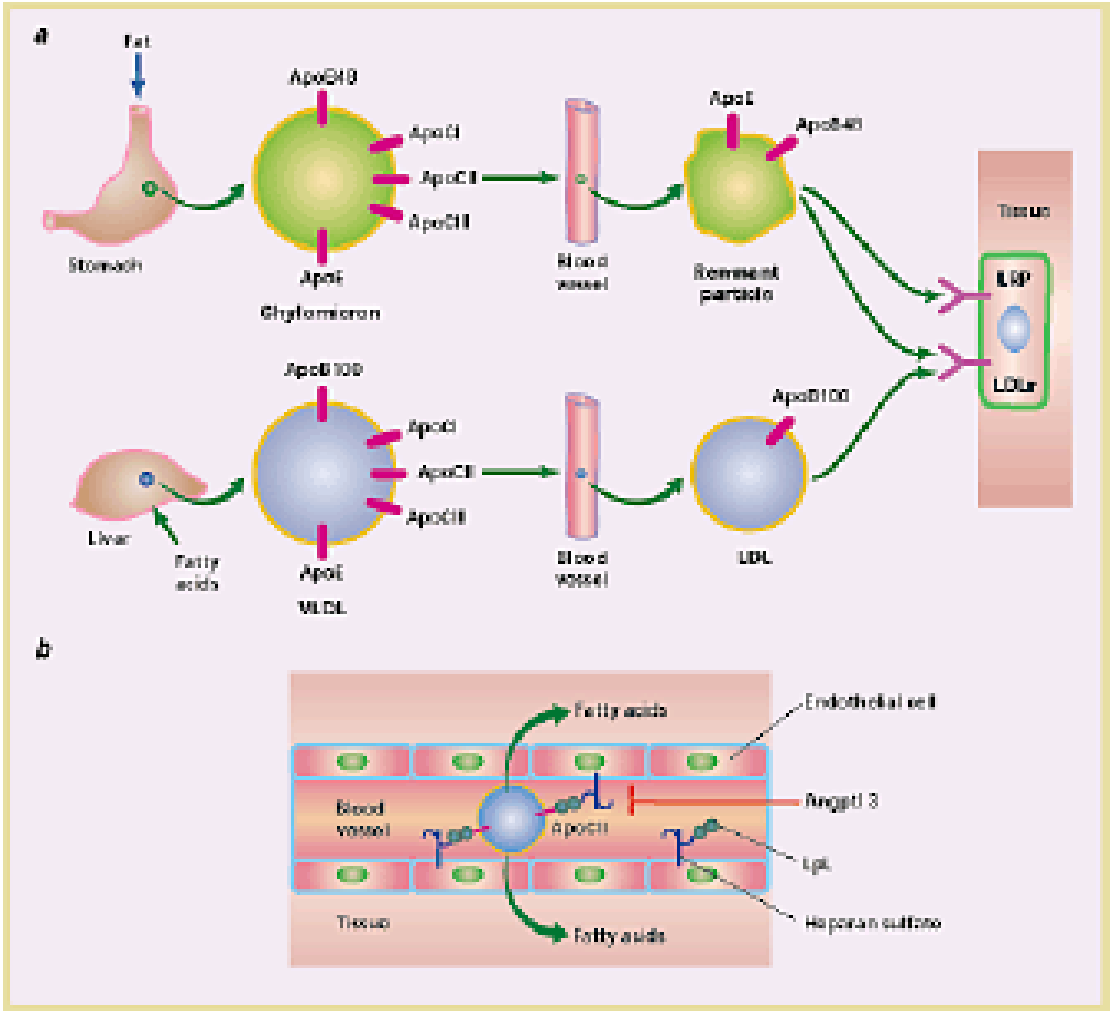
- **thrifty genotype hypothesis**
  - in the past, genes (allele of genes) providing higher levels of energy substrates (glucose, lipids, ...) but also those leading to increased energy stores (fat tissue), increased pro-thrombotic and pro-inflammatory potential offered selective advantage for their carriers → **genetic selection**
  - today, under less energy requiring conditions and with more or less unrestricted access to food (affluent societies) the same genes increase the likehood (risk) of developing the common "complex" diseases
    - **complex = genes + environment**
- genetics of lipid metabolism
  - due to the functional variability in the genes encoding e.g.
    - enzymes involved in lipid metabolism (both TAG and CH)
    - nuclear receptors (PPAR, RXR, LXR, ...)
    - apolipoproteins
    - receptors of apolipoproteins
    - hormonal control
      - glucocorticoids, thyroid hormones, ...
      - factors determining insulin sensitivity
        - utilisation of saccharides and lipids, esp. in insulin-sensitive tissues is mutually interconected and often ompetitive (☞ Randle's cycle)

Lipoprotein profiles – possible findings



Common atherogenic dyslipidemias

- polygenic hypercholesterolemia, fam. combined hyperlipidemia and diabetic dyslipidemia are the most common atherogenic HLPs
  - partly genetically determined (predisposed)
    - polygenic inheritance
  - dietary component
  - secondarily enhanced by insulin resistance (see further why)
- prognosis of combined hyperlipidemia is worse than that of hypercholesterolemia
- main features
  - impaired clearance of TAG by LPL (◮ insulin) from chylomicrons → increased TAG and increased delivery of TAG for liver
  - increased production of VLDL by liver (◮ insulin) from TAG, FFA from adipose tissue (◮ insulin) and glucose (◮ insulin)
  - therefore increased conversion of VLDL to LDL
  - low HDL



fat metabolism, especially. - activation of LPL - inhibition of HSL Inhibition of MK oxidation (+ ketogenesis) a formation of TAG and VLDL in the liver In diabetes du
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fat metabolism, especially. - activation of LPL - inhibition of HSL Inhibition of MK oxidation (+ ketogenesis) a formation of TAG and VLDL in the liver In diabete

Diabetic dyslipidemia

36

Insuline has important efect on: fat metabolism, especially:- activation of LPL,- inhibition of HSL Inhibition of MK oxidation (+ ketogenesis) a formation of TAG and VLDL in the liver

In diabetes due to a deficiency insulin (T1DM) or resistence (T2DM) this effect is missing, respectively.

disorder and lipid metabolism

- primarily TAG, - Secondarily also CH overproduction VLDL (and thus LDL) and increase catabolism HDL

and secondarily further deterioration use of glucose because of metabolism of sugars and fats together closely related: competitions of Glc and MK at level intermediary metabolism

diabetic dyslipidemia is therefore

- **atherogenic** because it increases supply CH and worsens reverse transport CH
- **pro-diabetic**, because it worsens sensitivity to insulin

Classification (?) vs. reality(!)

genetic predisposition ("thrifty" genes)
(enzymes, apolipoproteins, receptors, transcription factors, ...)

dietary fat (TAG and CH) intake

some genes predisposing to diabetes and dyslipidemia are clustered within the trait called METABOLIC SYNDROM

complex, combined
DYSLIPIDEMIA
with familiar and secondary components
leading to variably increased
atherosclerosis risk

inzulin resistance / diabetes mellitus
(unsuppressed lipolysis, glucose and FFA delivery to the liver)

Secondary HLPs

- caused by other primary disease, nevertheless its impact on **cardiovascular system is the same** as in primary HLPs
- treatment involves either primary disease and hypolipidemic drugs
- unlike primary ones, secondary HLPs respond well to **dietary interventions**

Cause	Elevation
Diabetes mellitus (type 1)	↑TAG, ↓ HDL
Hypothyreosis	↑CH
Nephrotic syndrome	↑CH, TAG
Chronic renal insufficiency	↑TG
Cholestasis	↑CH

Hypolipoproteinemia

Abetalipoproteinemia- AR rare hereditary DMP, completely lacking lipoprotein particles containing ApoB (chylomicrons, VLDL), the overall level of CHOL and TAG are low, fat malabsorption, steatorrhoea, stunted growth later formed retinitis pigmentosa and cerebellar

Ataxia is typical acanthocytosis (stratum erythrocytes) deficit of fat-soluble vitamins, impaired cortisol lipids accumulate in the epithelium, gut - vakuoalizace, the body lacks essential MK (linoleic acid)

Analfalipoproteinemie (Tangier disease) decreased levels of HDL and ApoA-I, also lower LDL and total CHOL, HDL does not pass ApoCII → just VLDL, CHOL esters accumulation in tissues, yellowish enlarged tonsils, hepatosplenomegaly and corneal infiltration, higher incidence of the AT

Familial hypolipoproteinemia associated with longevity, probably for the low incidence of myocardial infarction. It is still considered a rare genetic, abnormality, probably with autosomal dominant inheritance. LDL cholesterol levels are reduced below 5 th percentile threshold normal range.

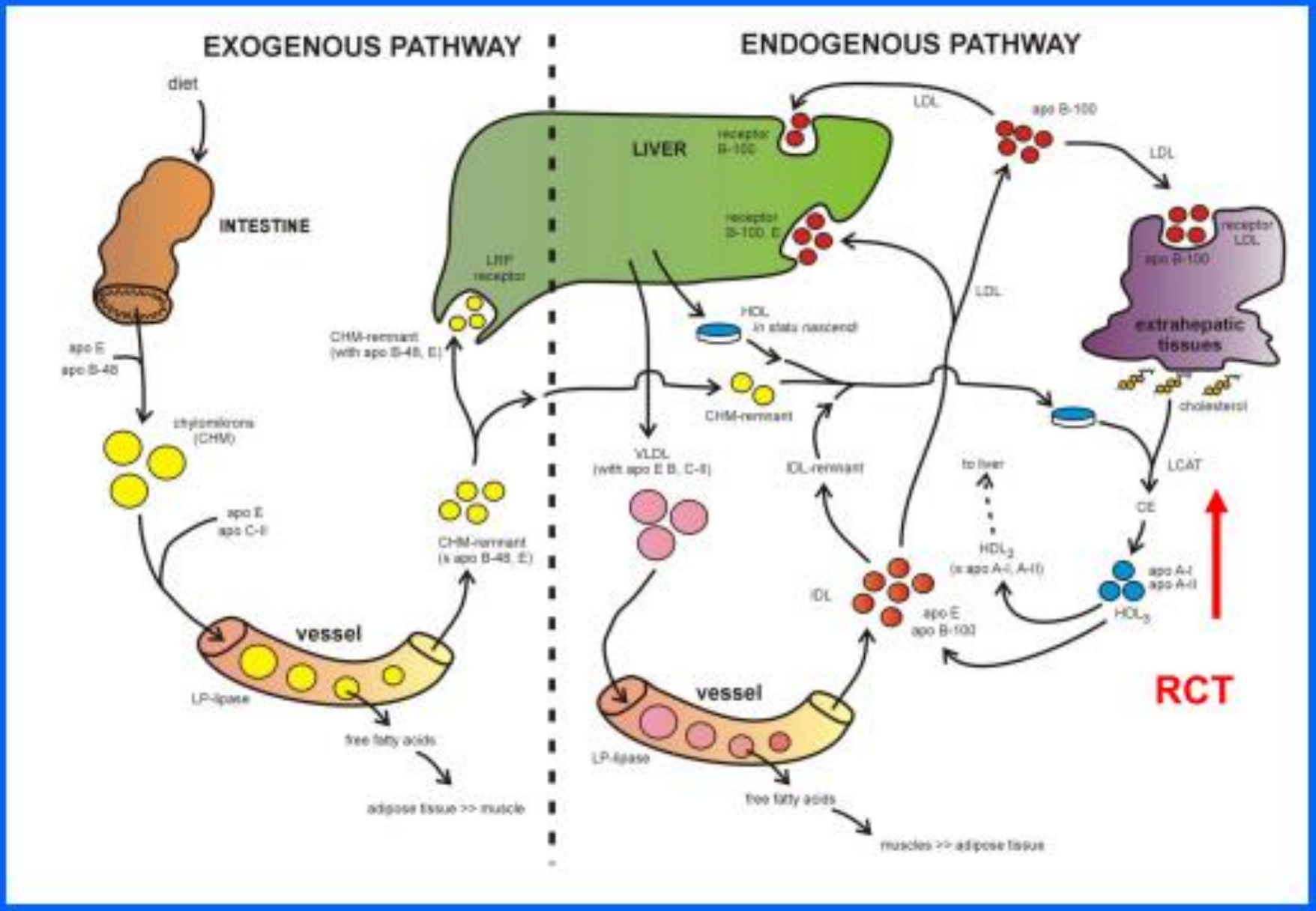
familial hypoalphalipoproteinemia

It is a genetic lipoprotein abnormalities associated with the occurrence of longevity in the family (about 8 to 12 years compared to the average in the population); expected form of inheritance is autosomal dominant. Familial forms, however, be distinguished from forms obtained (secondary) eg. when you abuse alcohol or use contraceptive preparations or preparations based estrogens. The syndrome is characterized by significant increasing the HDL cholesterol-1 lipoprotein to ELFO), mild to moderate increase celkového (increased cholesterol in plasma and normal concentrations of S-triglycerides. Are multiplied HDL particles containing only ApoAI not containing particles as ApoAI and ApoAII

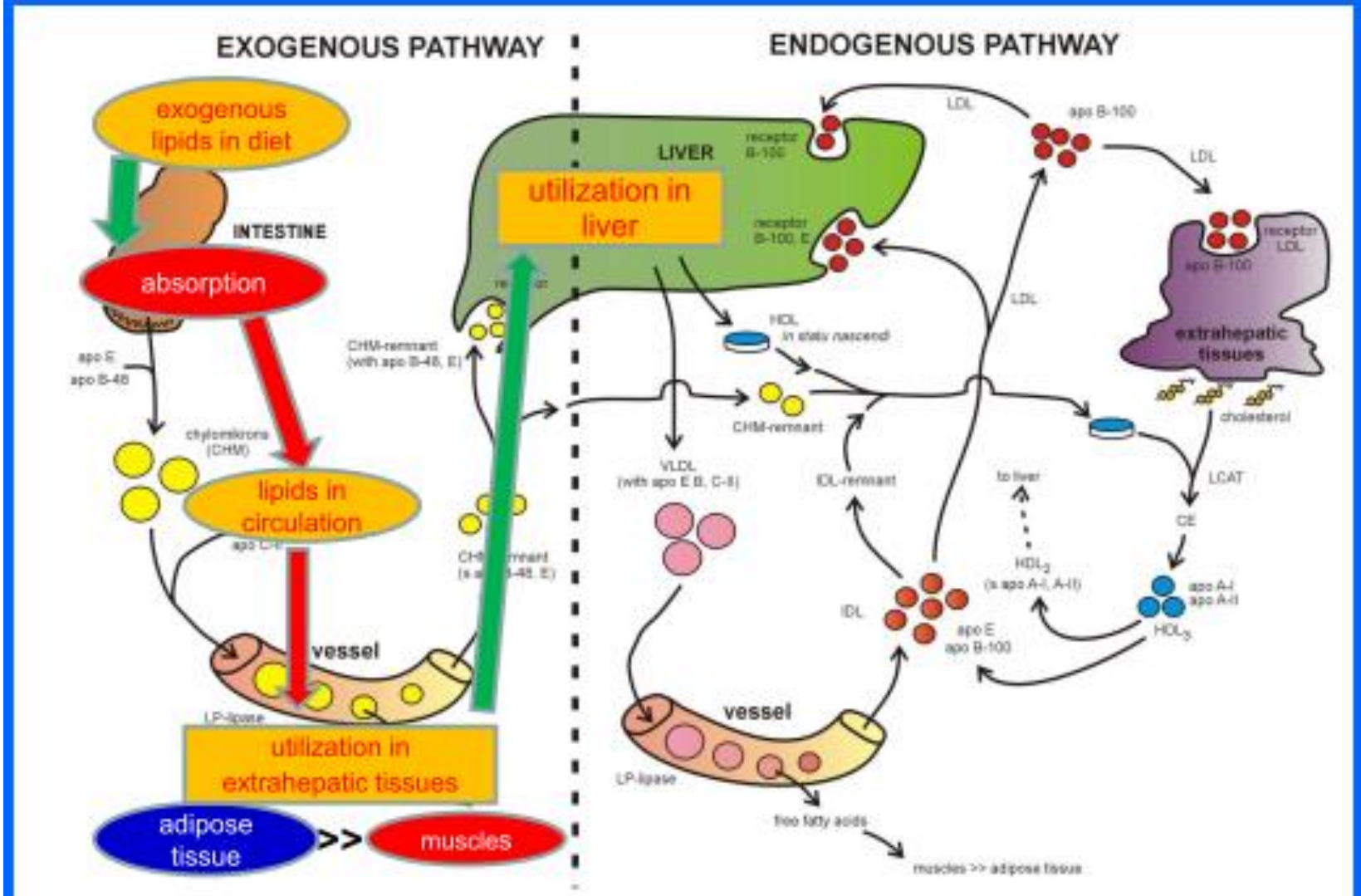
[LPA I And II]. Abnormality is probably due to increased synthesis of apo AI. There is a reduced risk of cardiovascular disease

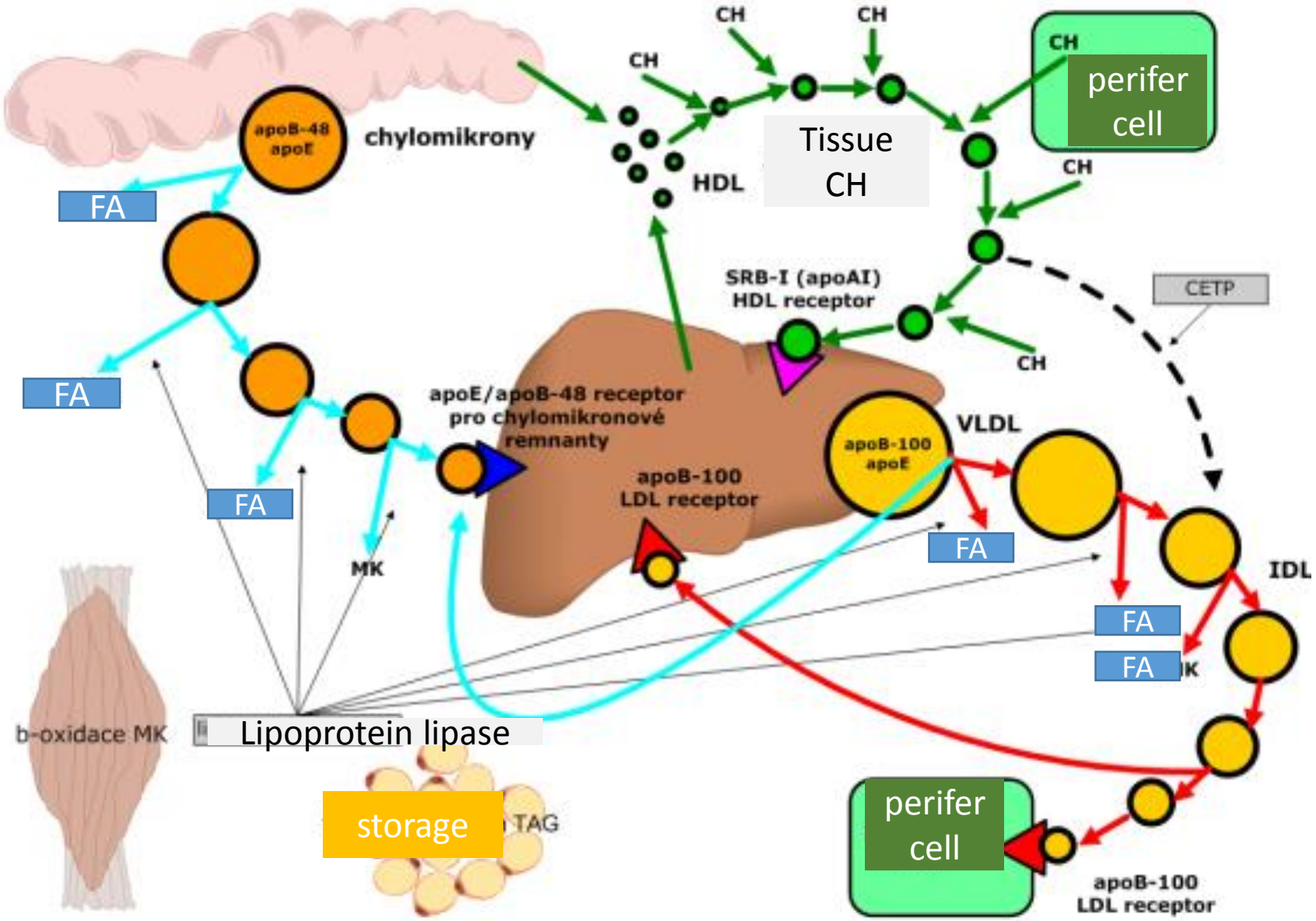
induced atherosclerosis.

Metabolic lipoprotein pathway

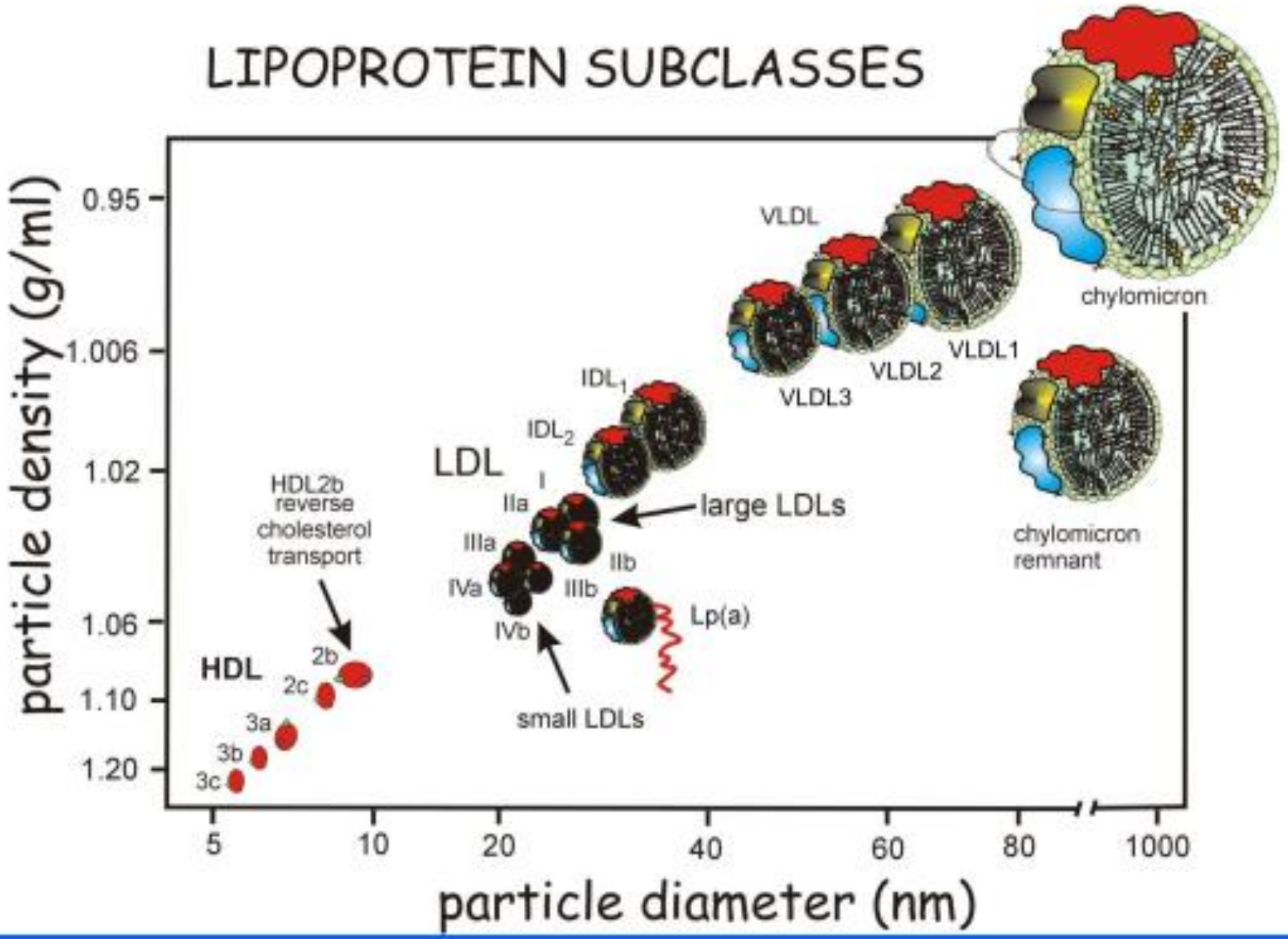


Metabolic lipoprotein pathway

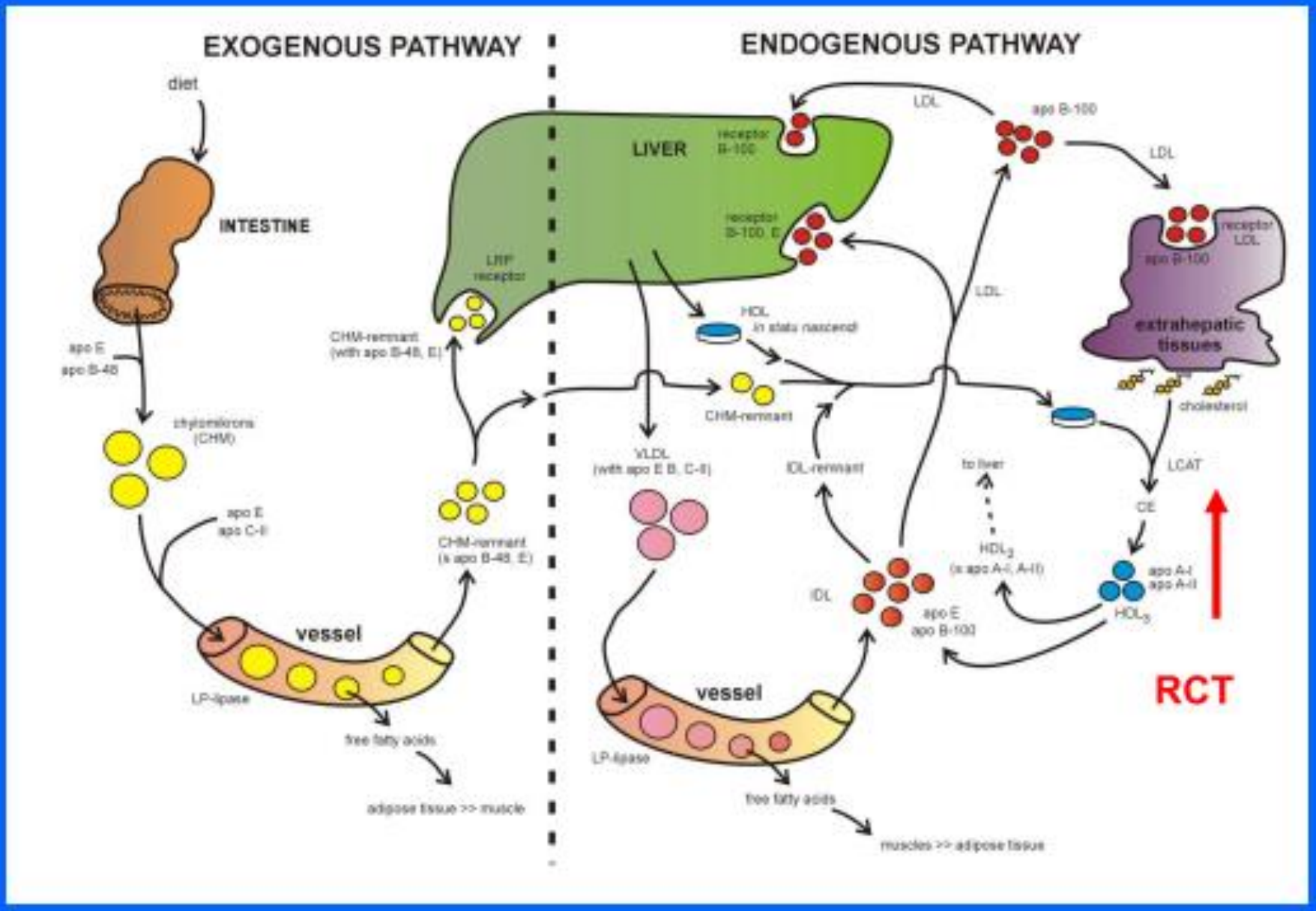



CH
CH
CH
CH
CH
perifer cell
apoB-48 apoE
chylomikrony
HDL
Tissue CH
FA
FA
FA
SRB-I (apoAI) HDL receptor
CETP
CH
apoE/apoB-48 receptor pro chylomikronové remnanty
apoB-100 LDL receptor
apoB-100 apoE
VLDL
FA
IDL
FA
FA
MK
b-oxidace MK
Lipoprotein lipase
storage
TAG
perifer cell
apoB-100 LDL receptor

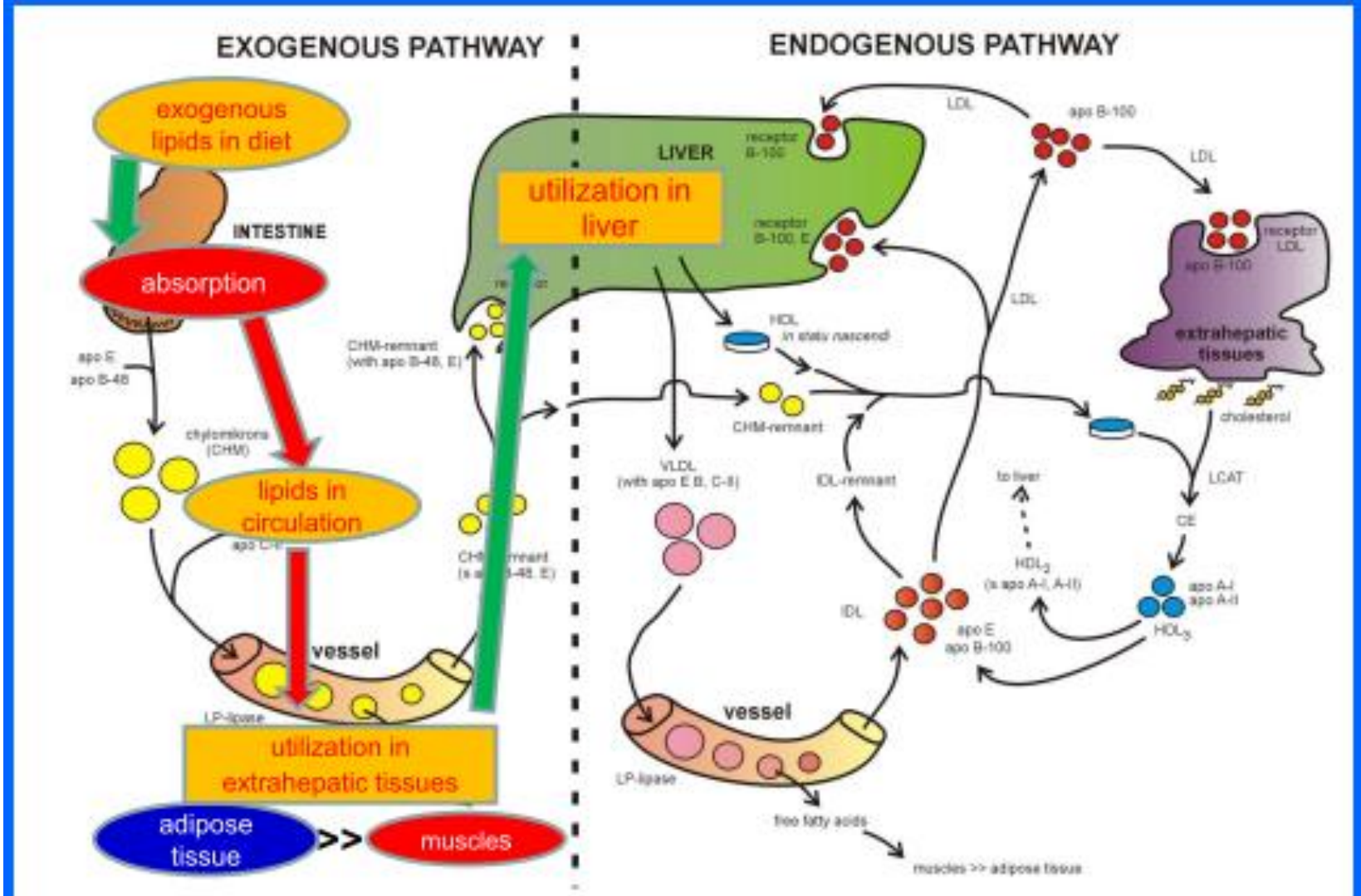
Lipoprotein size

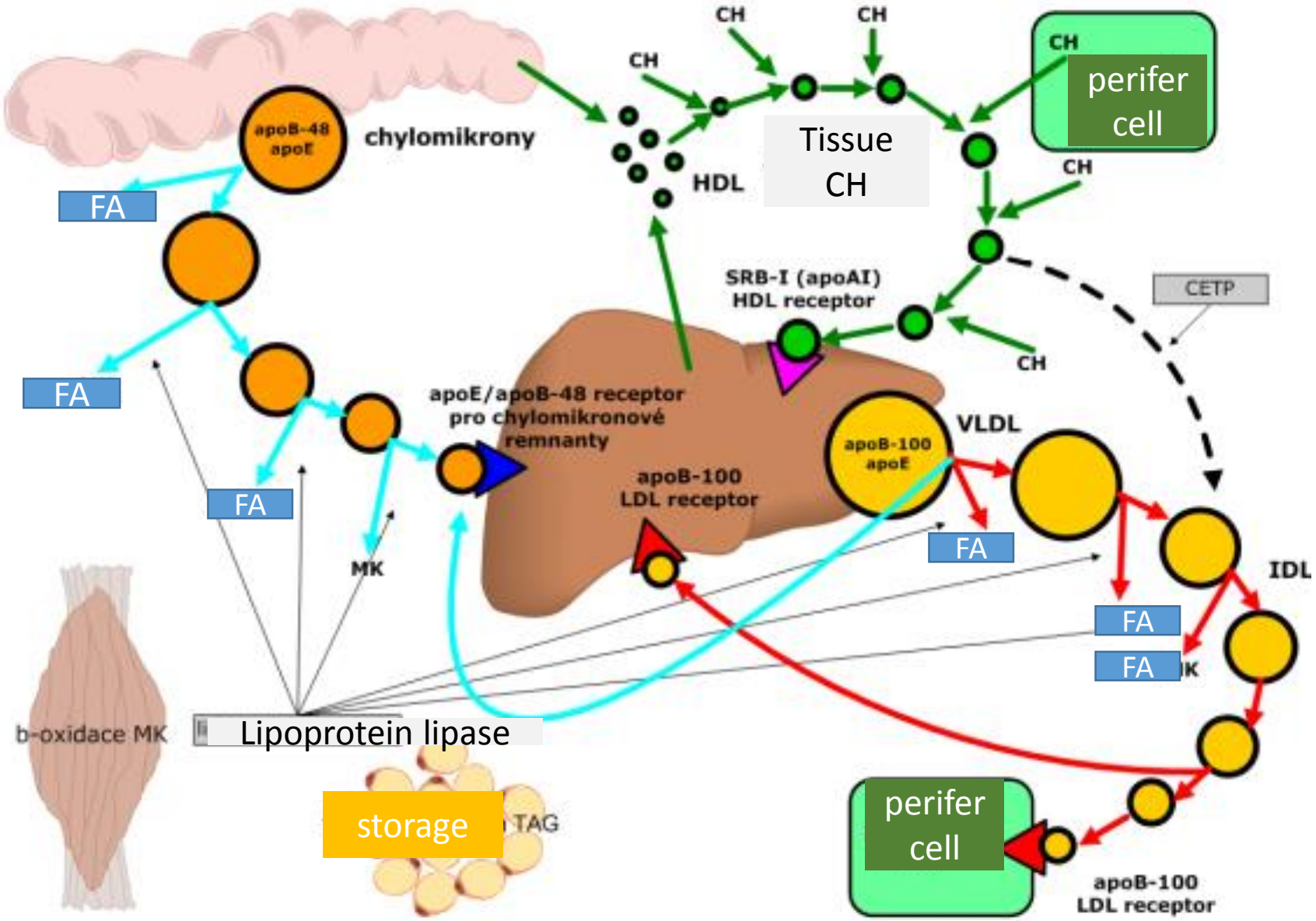


Metabolic lipoprotein pathway



Metabolic lipoprotein pathway




CH
CH
CH
CH
CH
perifer cell
apoB-48 apoE
chylomikrony
HDL
Tissue CH
FA
FA
FA
SRB-I (apoAI) HDL receptor
CETP
CH
apoE/apoB-48 receptor pro chylomikronové remnanty
apoB-100 LDL receptor
apoB-100 apoE
VLDL
FA
IDL
FA
FA
MK
b-oxidace MK
Lipoprotein lipase
storage
TAG
perifer cell
apoB-100 LDL receptor

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

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
$C\text{-}III_{0\text{-}3}$	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 - triacylglycerol, CM_R - remnant CM, ß-VLDL – remnant VLDL staying in plasma

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

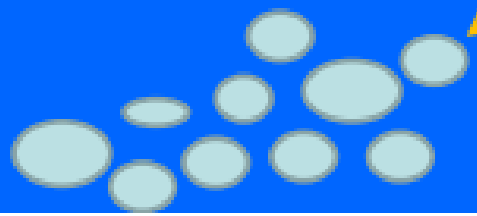
Gastric lipase (pH optimum 3.5-5.4)

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

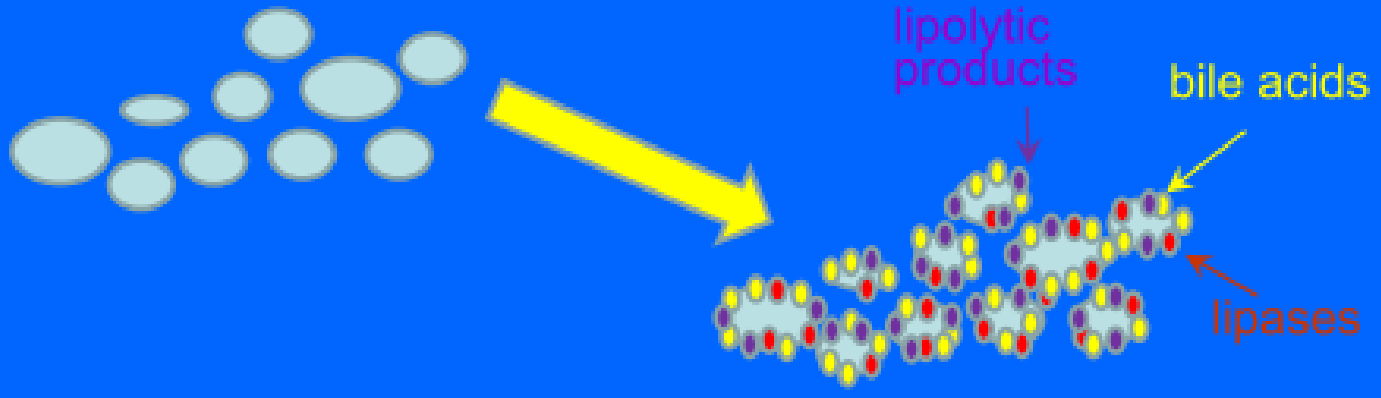
intestinal phase - pancreatic lipases

alkaline sphingomyelinase

SPH → Cer + P-choline

neutral ceramidase

Cer → sphingosine + FFA

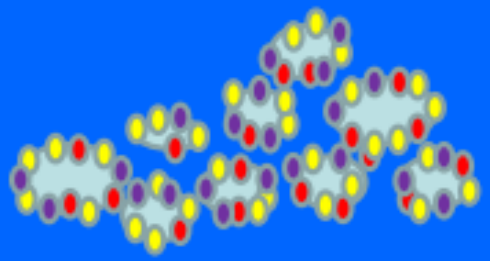


2. lipolysis of lipids

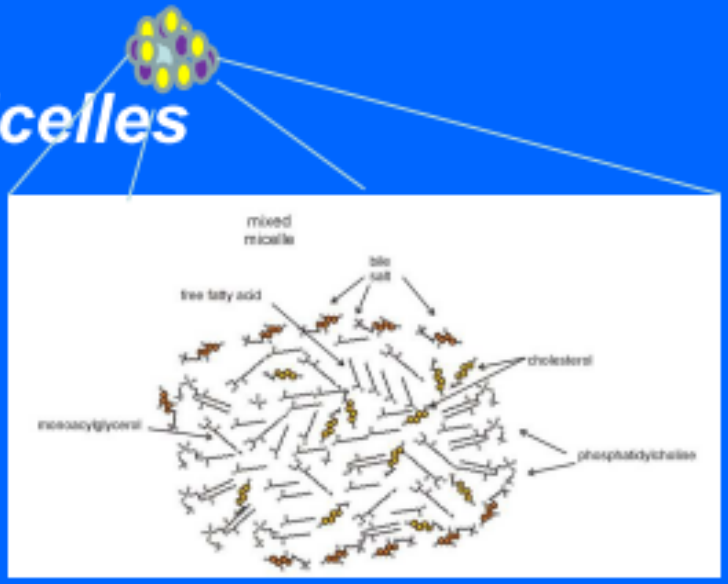
Lipid digestion

intestinal phase - formation of micelles

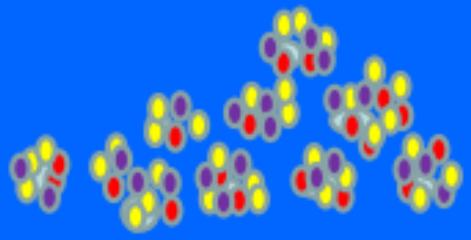
BA and PL displace lipolysis products from the water-oil interface



mixed micelles

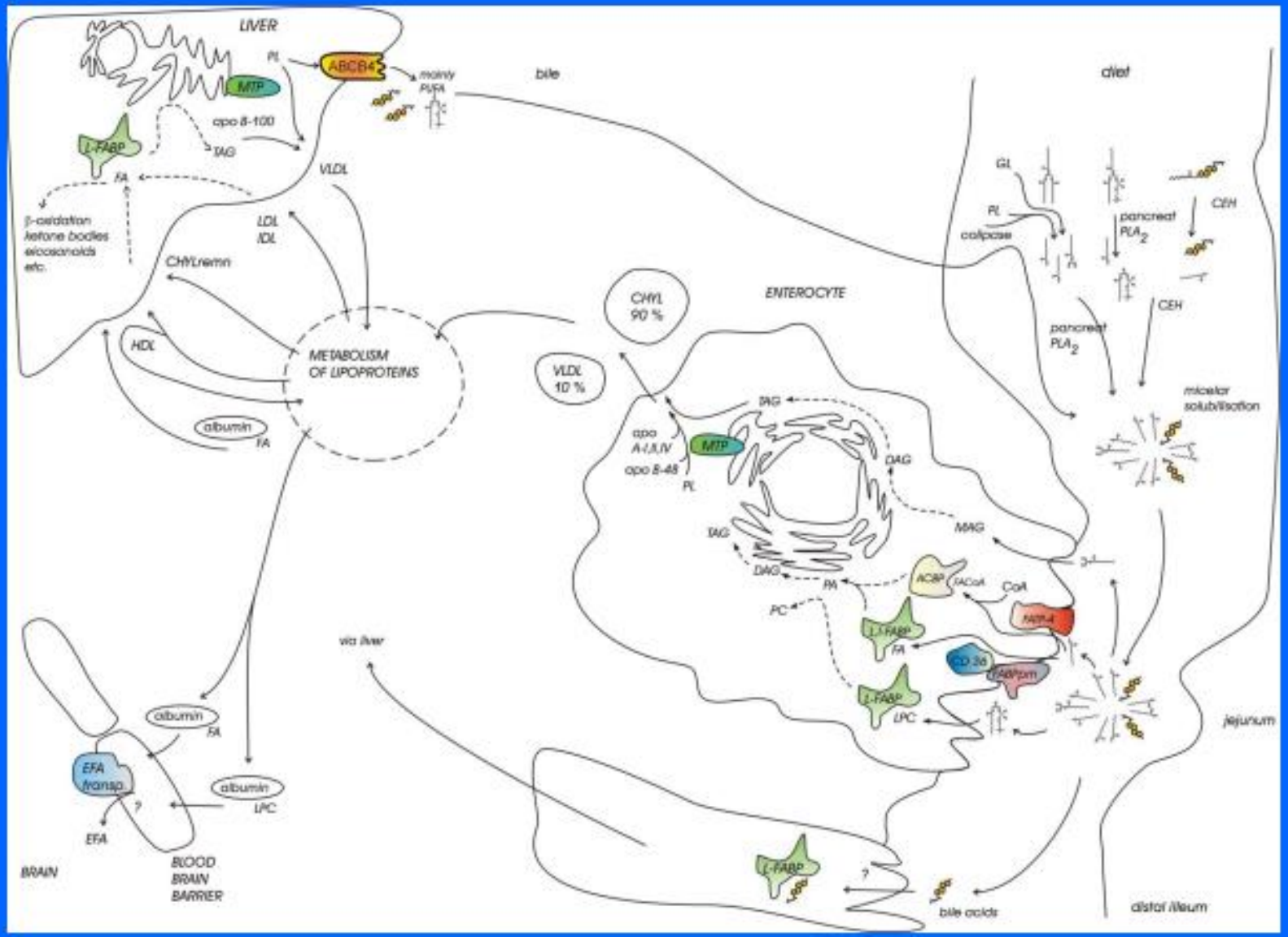


further lipolysis by lipases

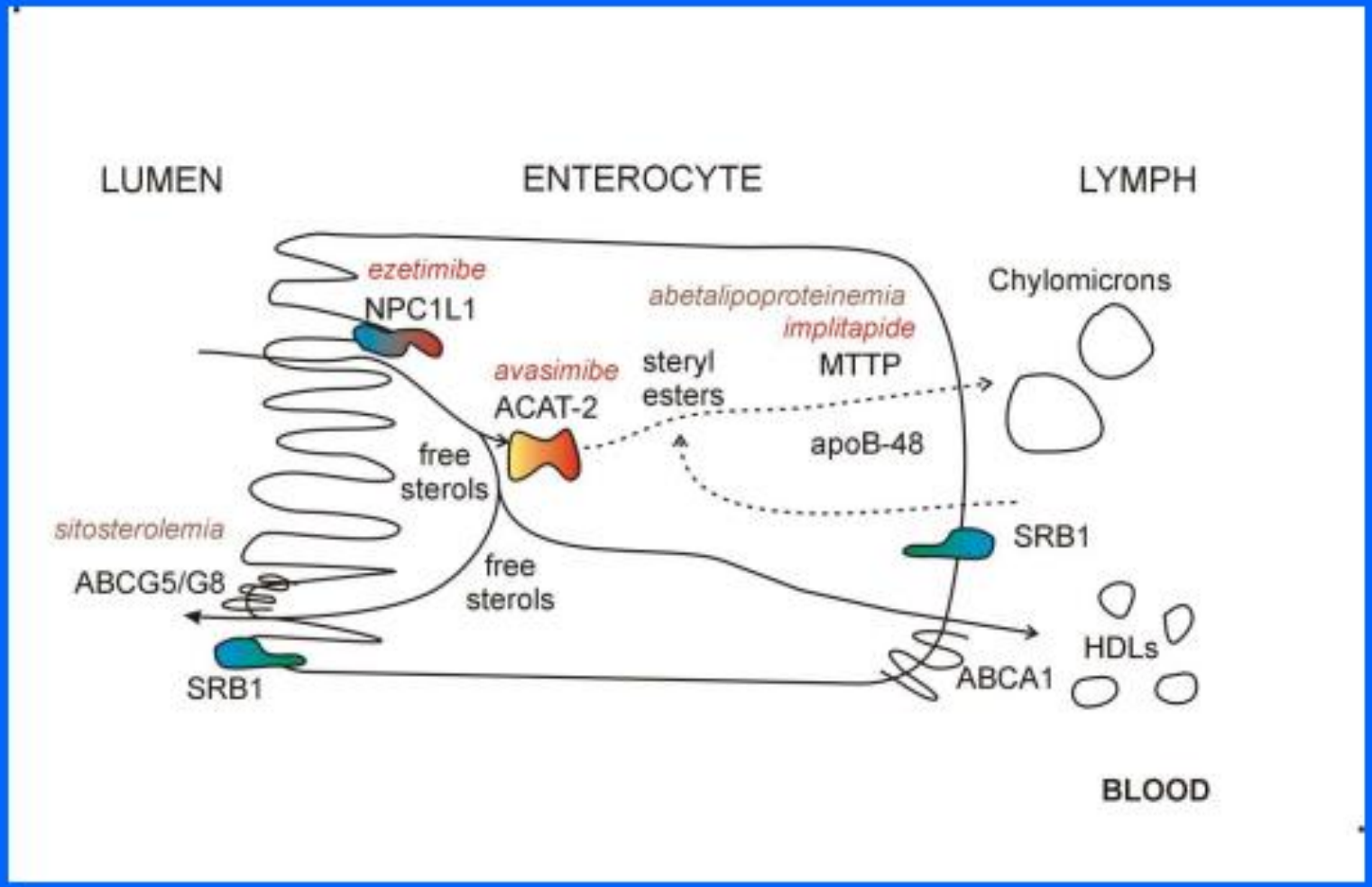


3. solubilization of lipids

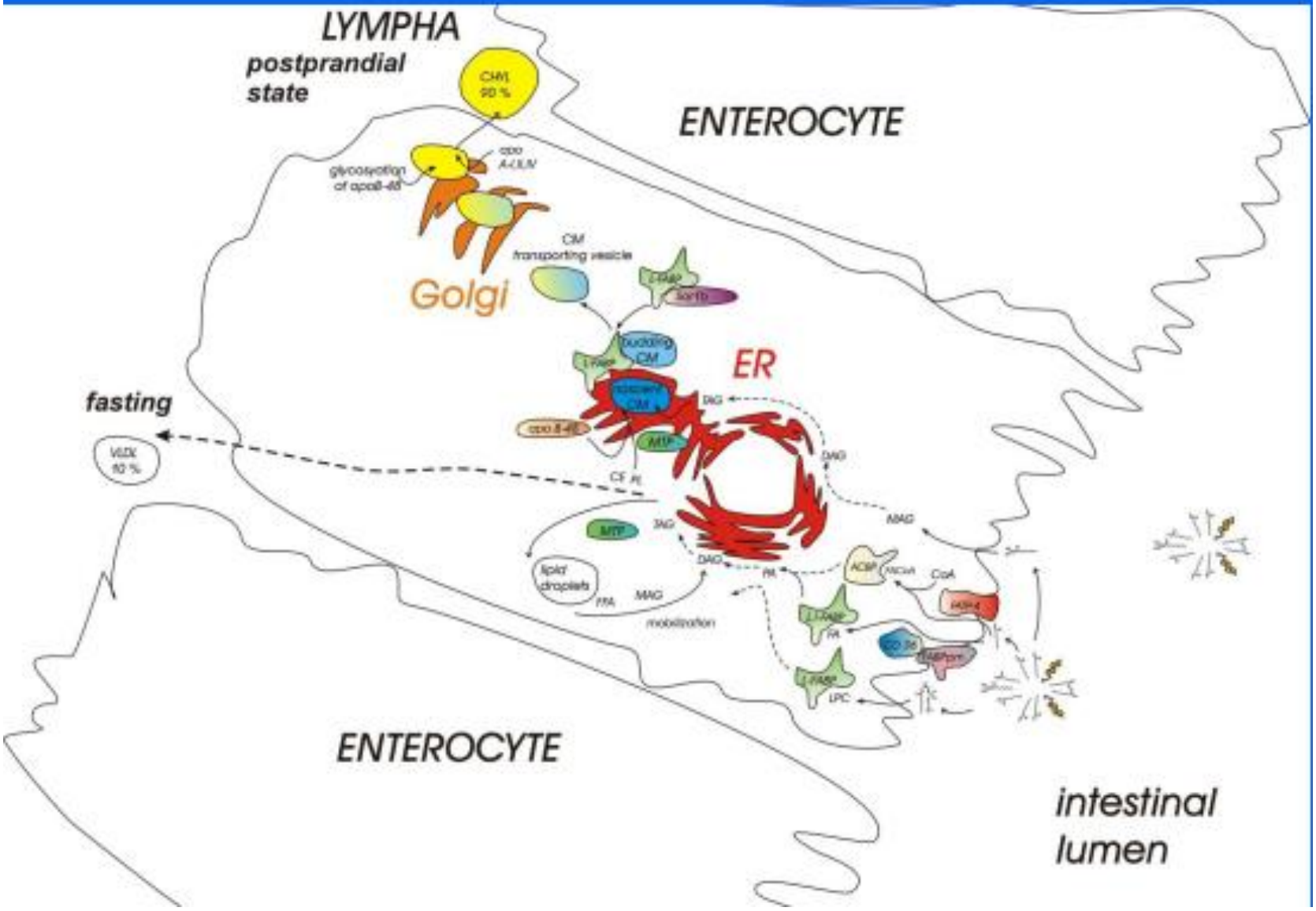
Lipid absorption – fatty acids



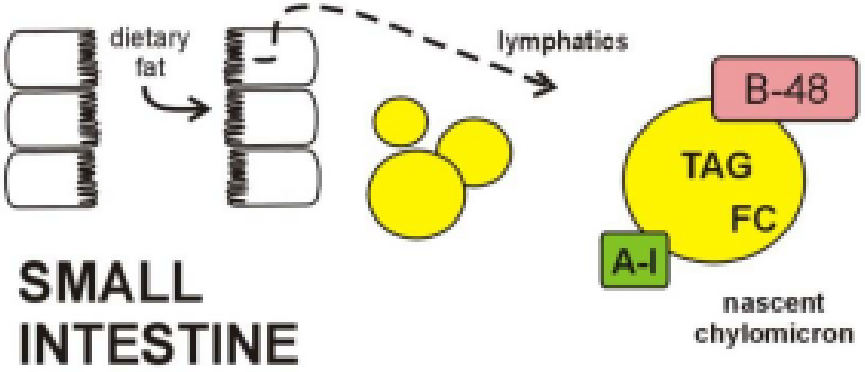
Lipid absorption – sterols



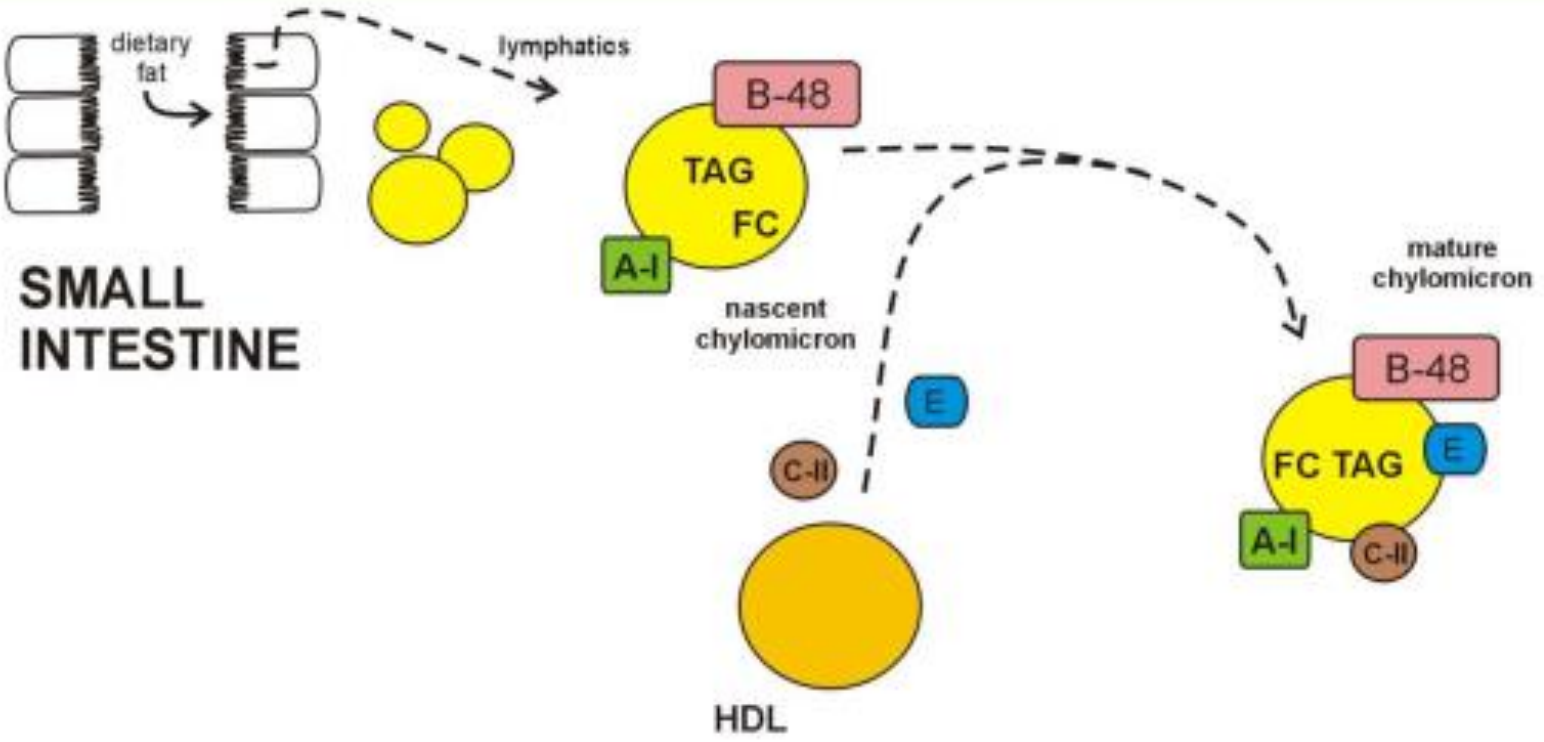
Assembly of chylomicrons



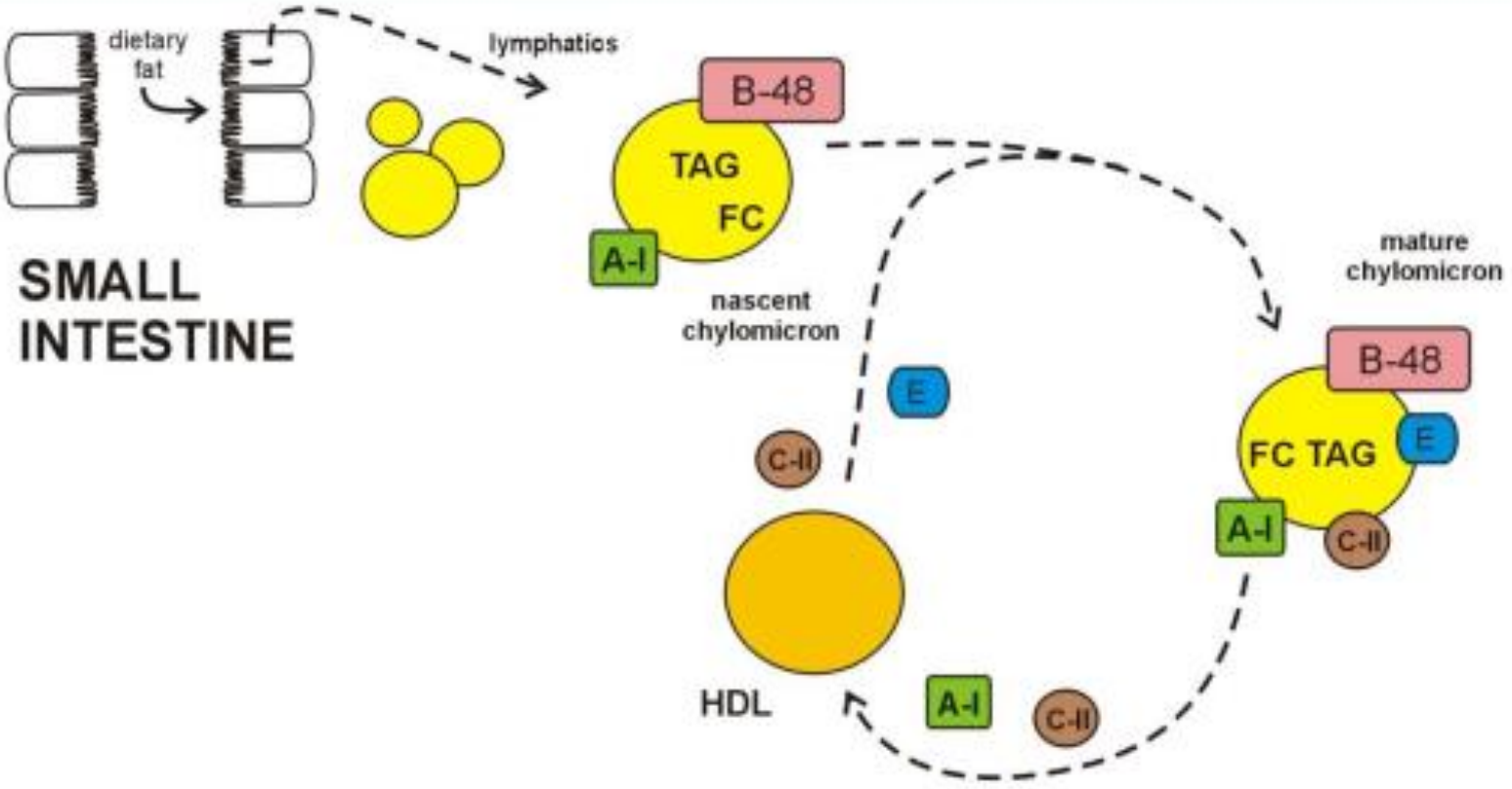
Chylomicrons



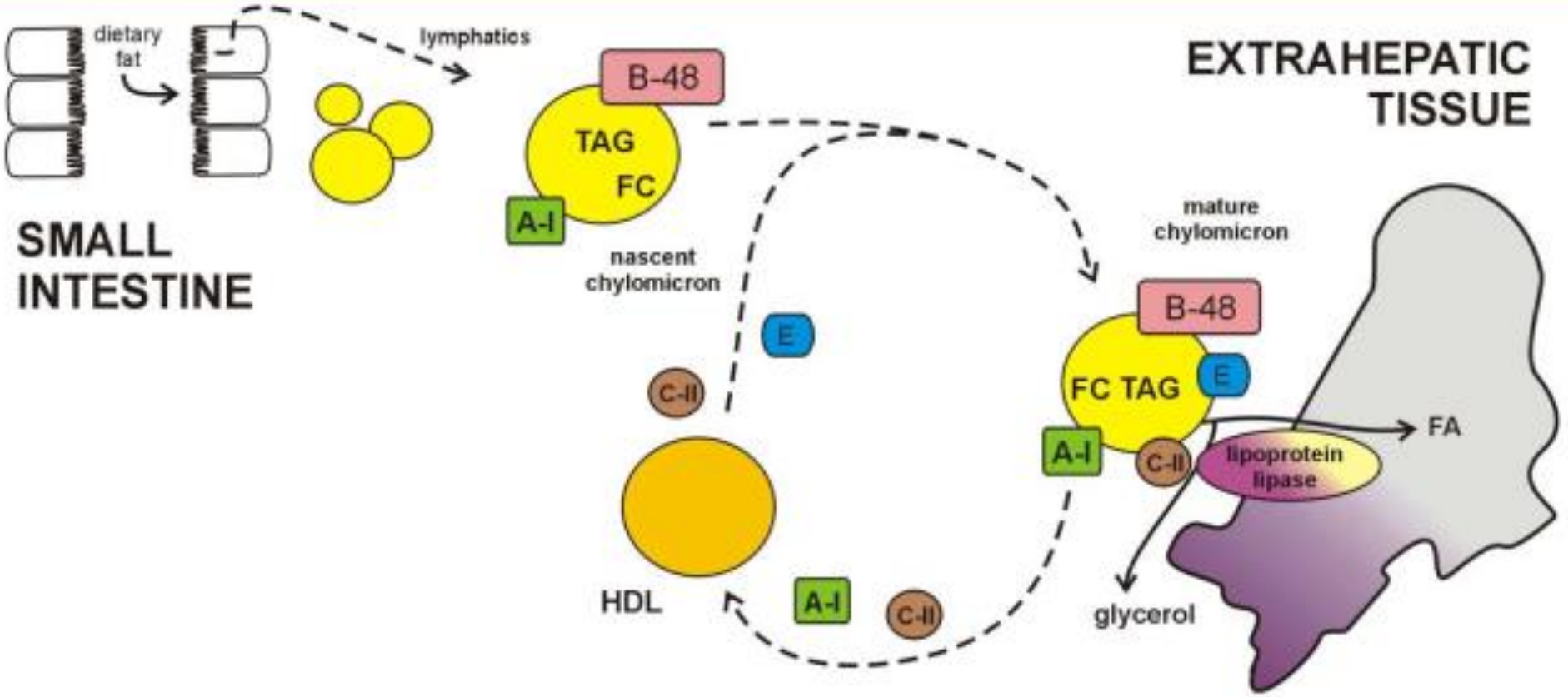
Chylomicrons



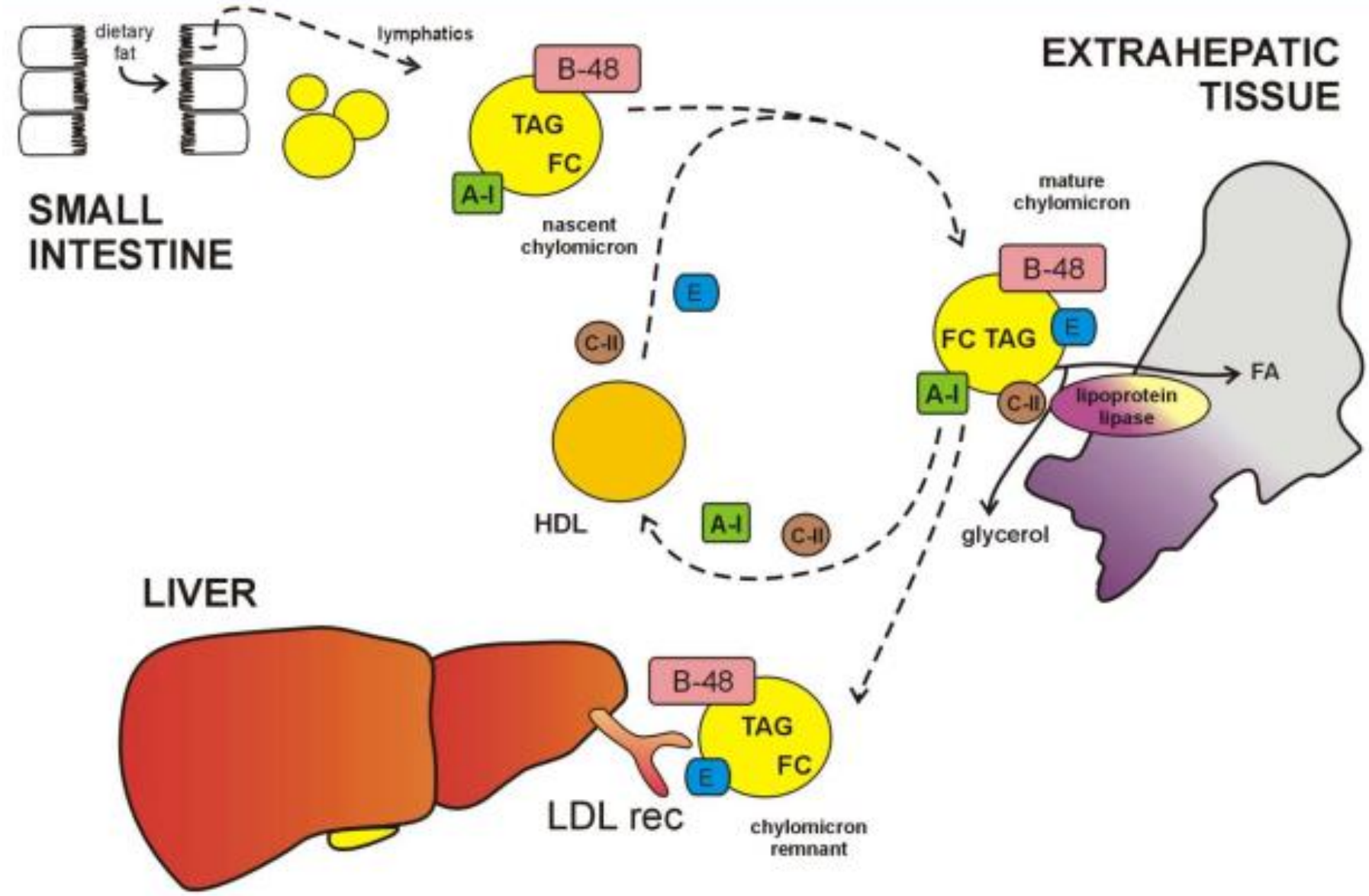
Chylomicrons



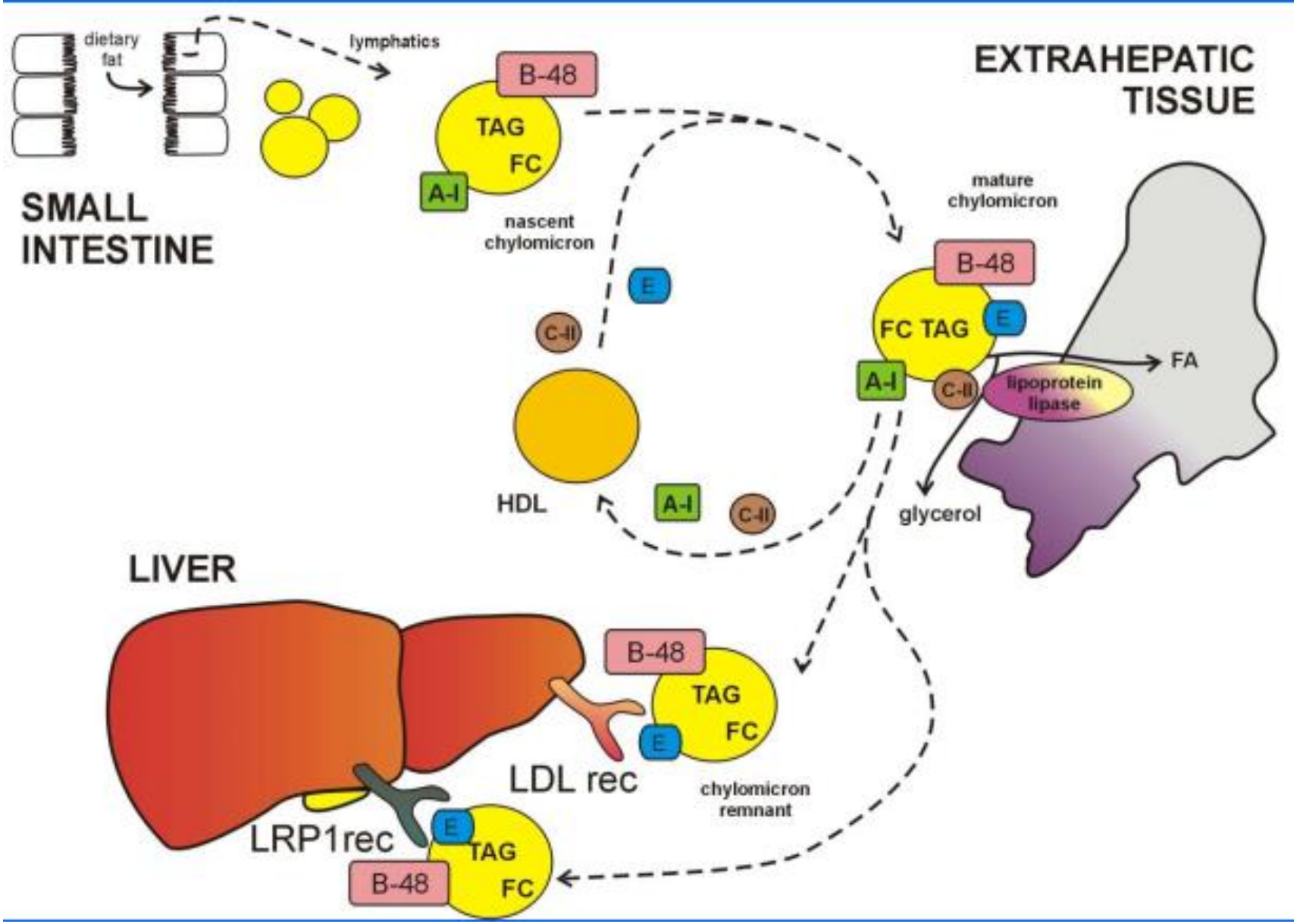
Chylomicrons



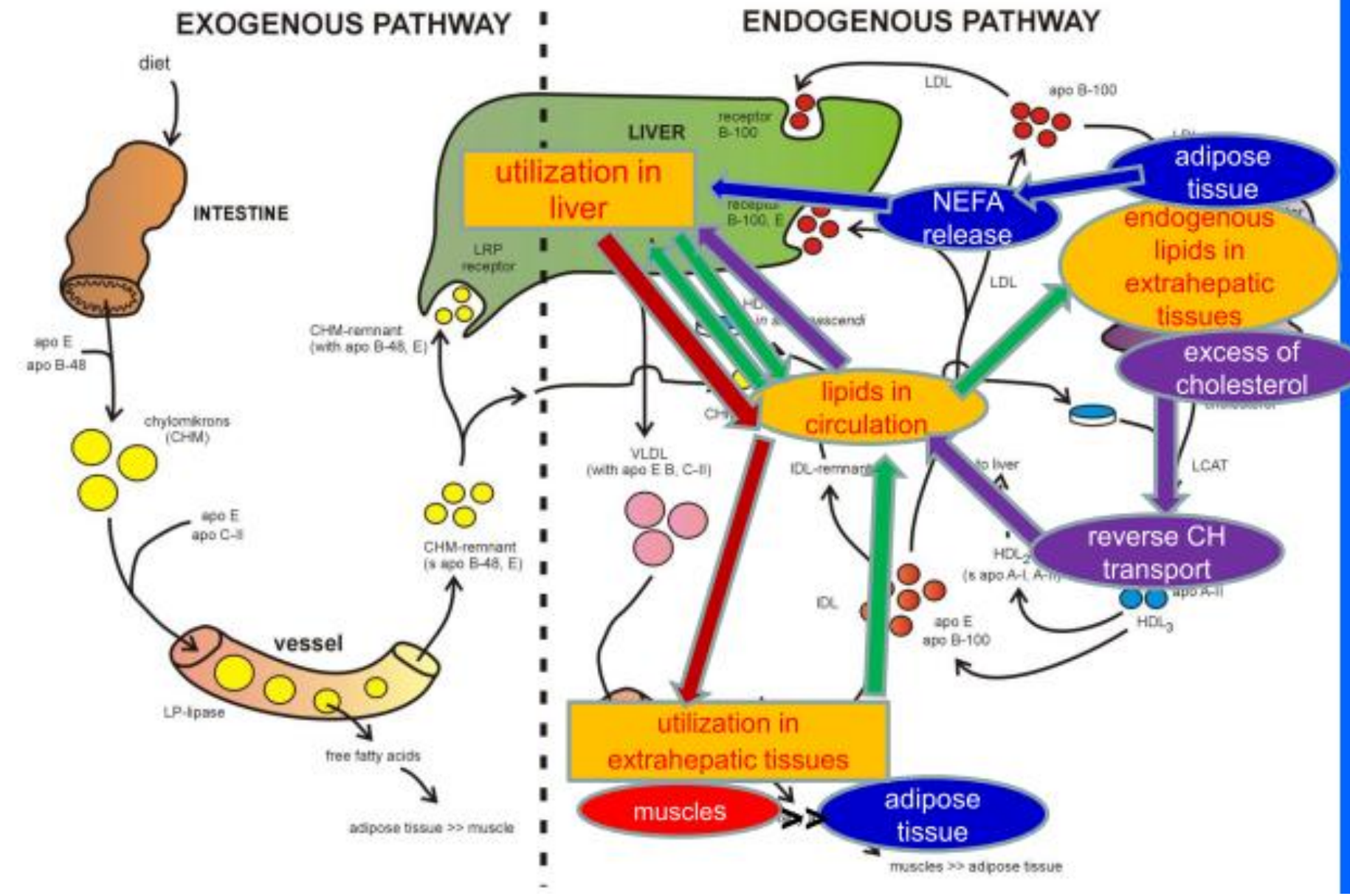
Chylomicrons



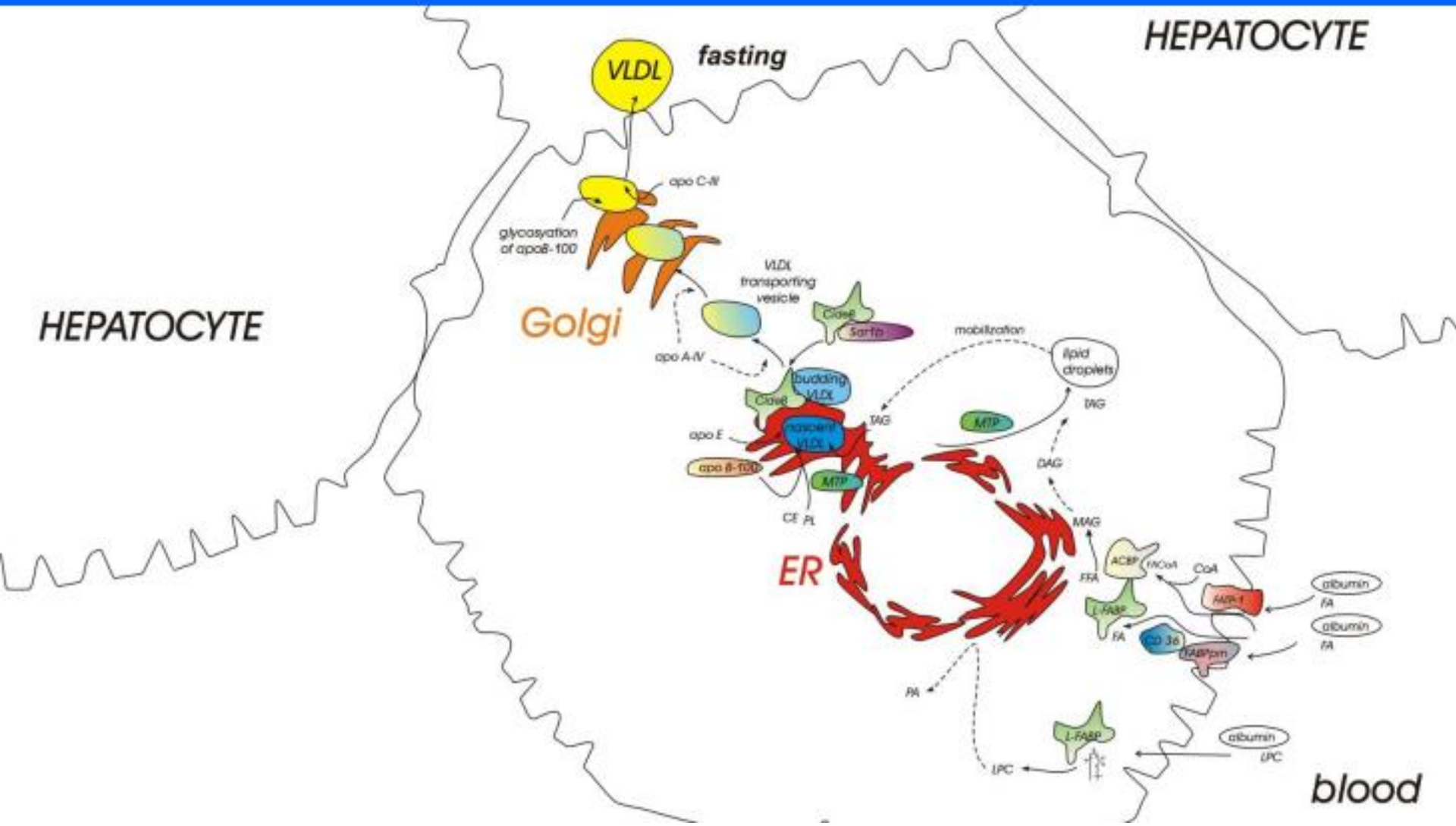
Chylomicrons



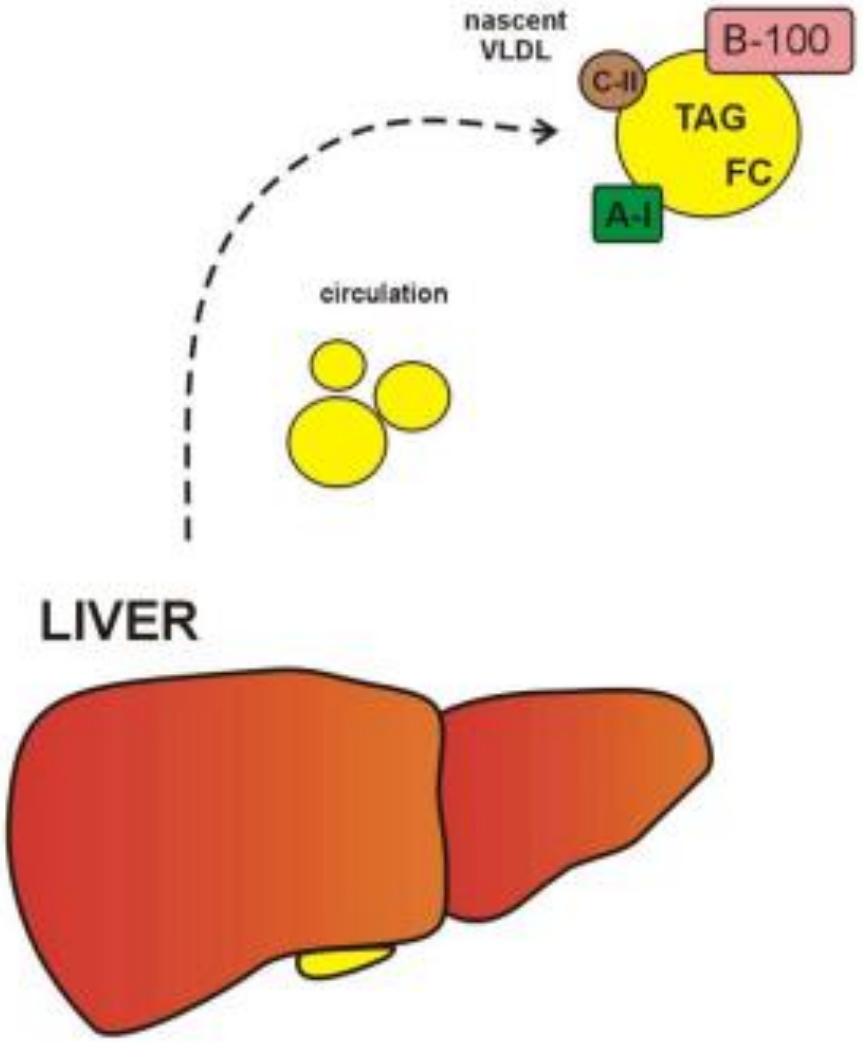
Metabolic lipoprotein pathway



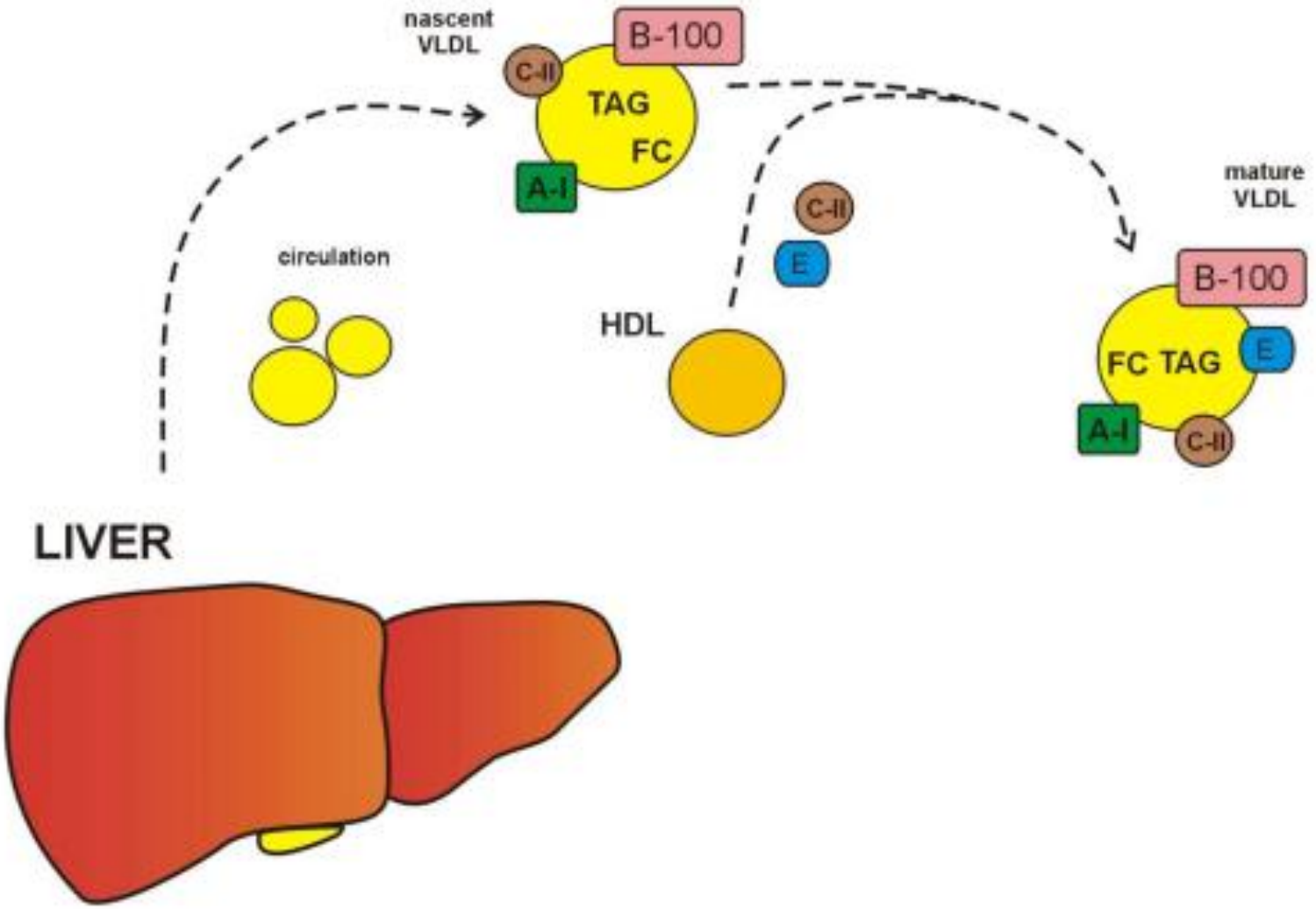
Assembly of VLDL



Fate of VLDLs



Fate of VLDLs



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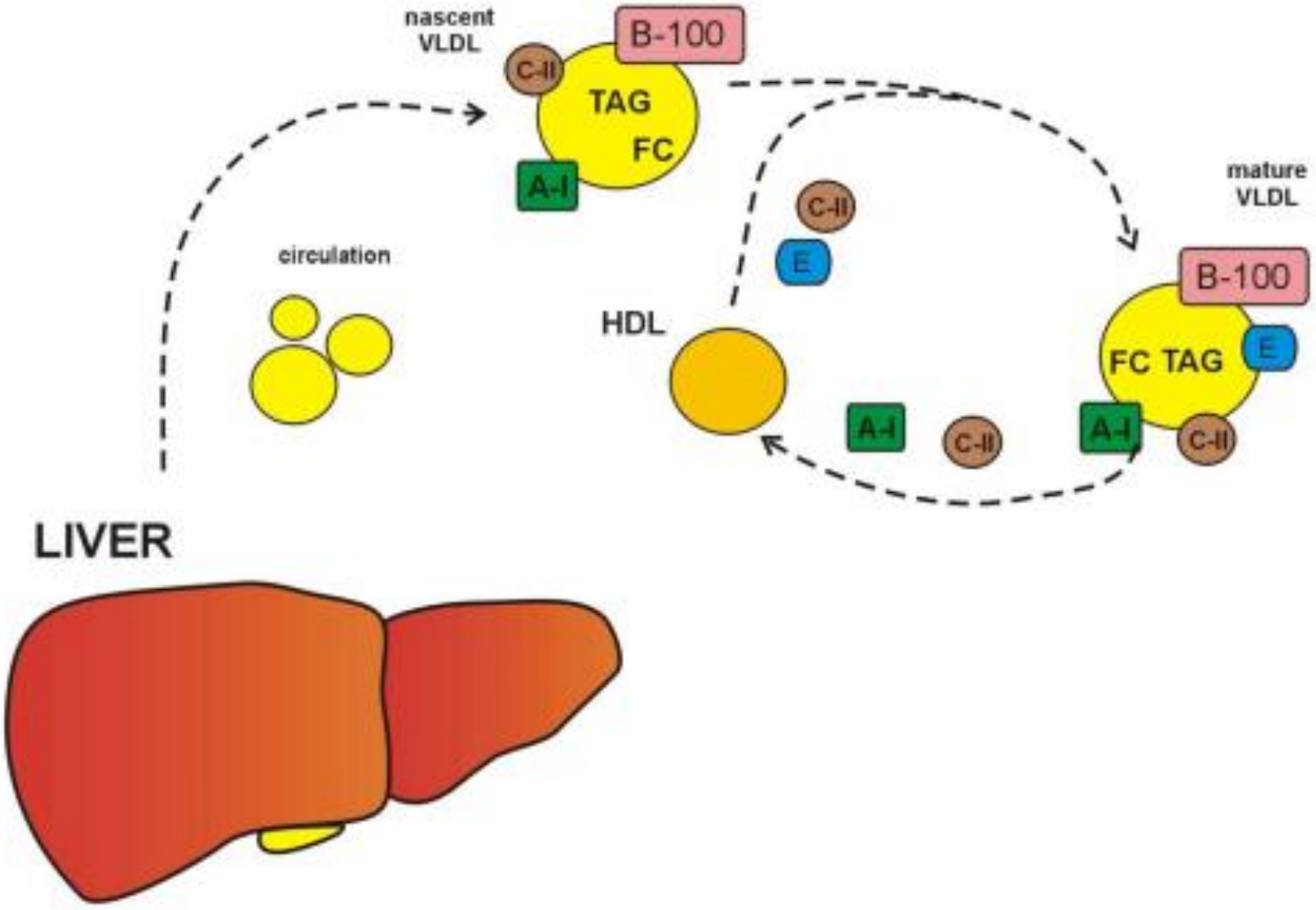

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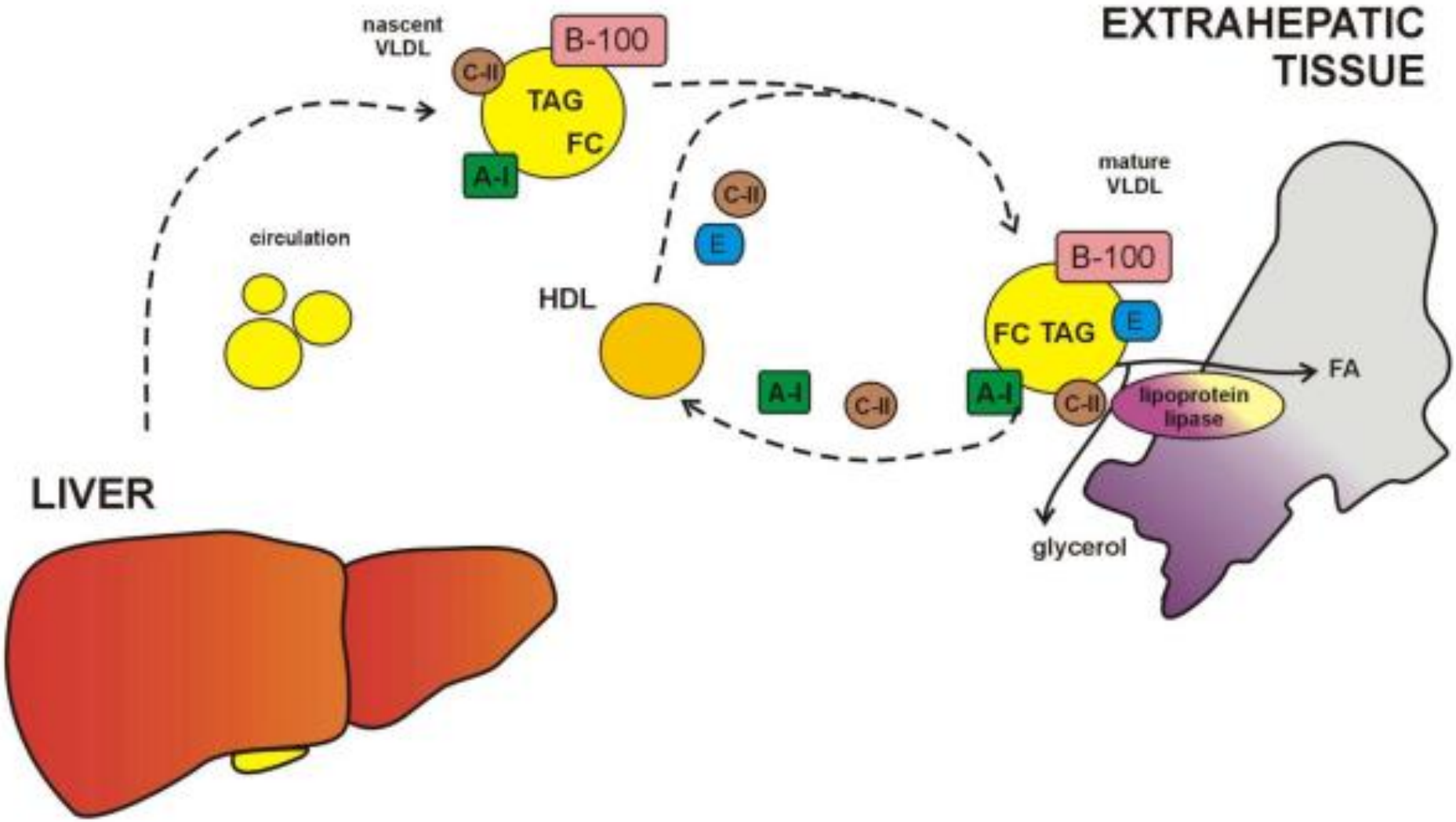
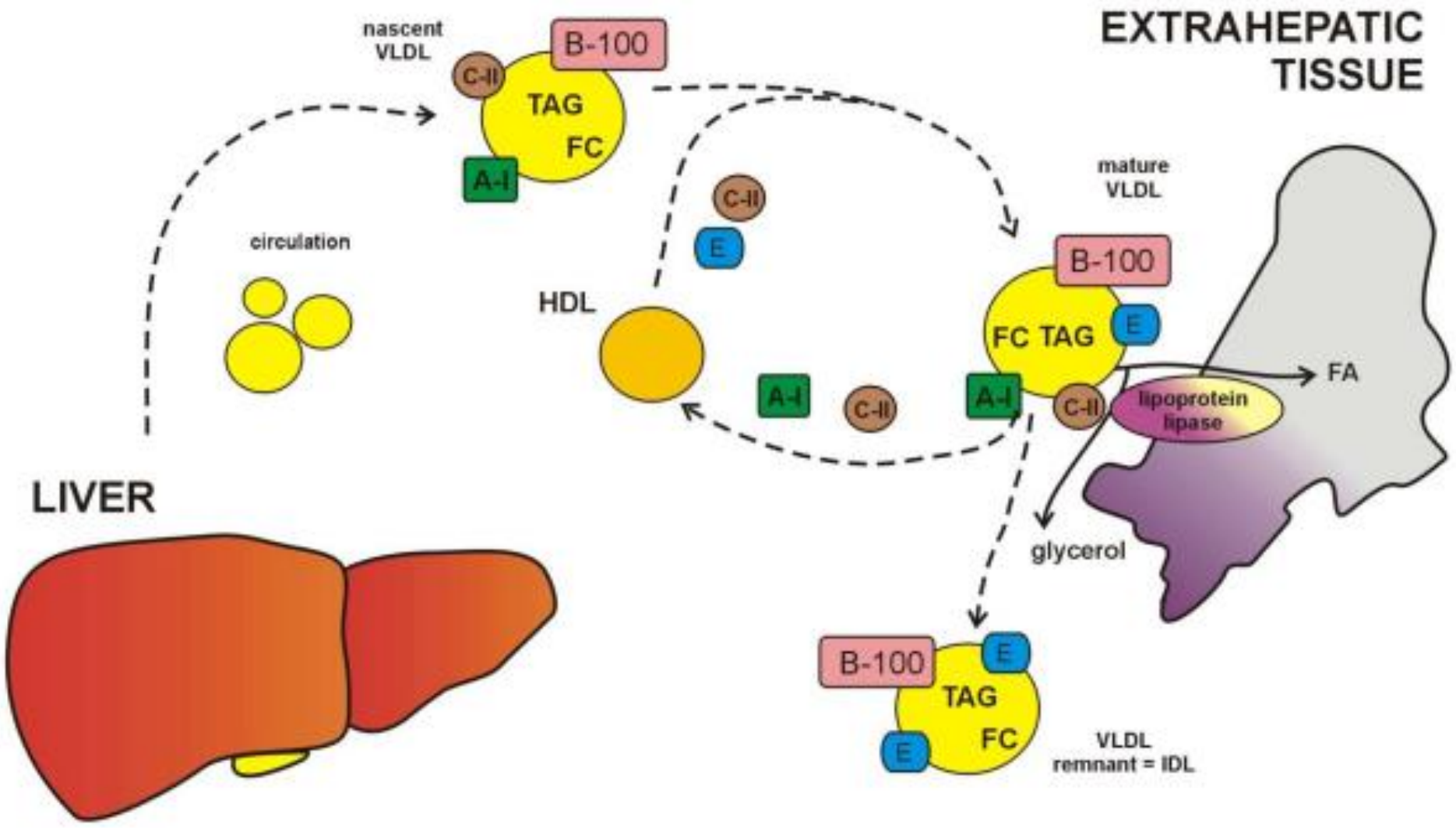
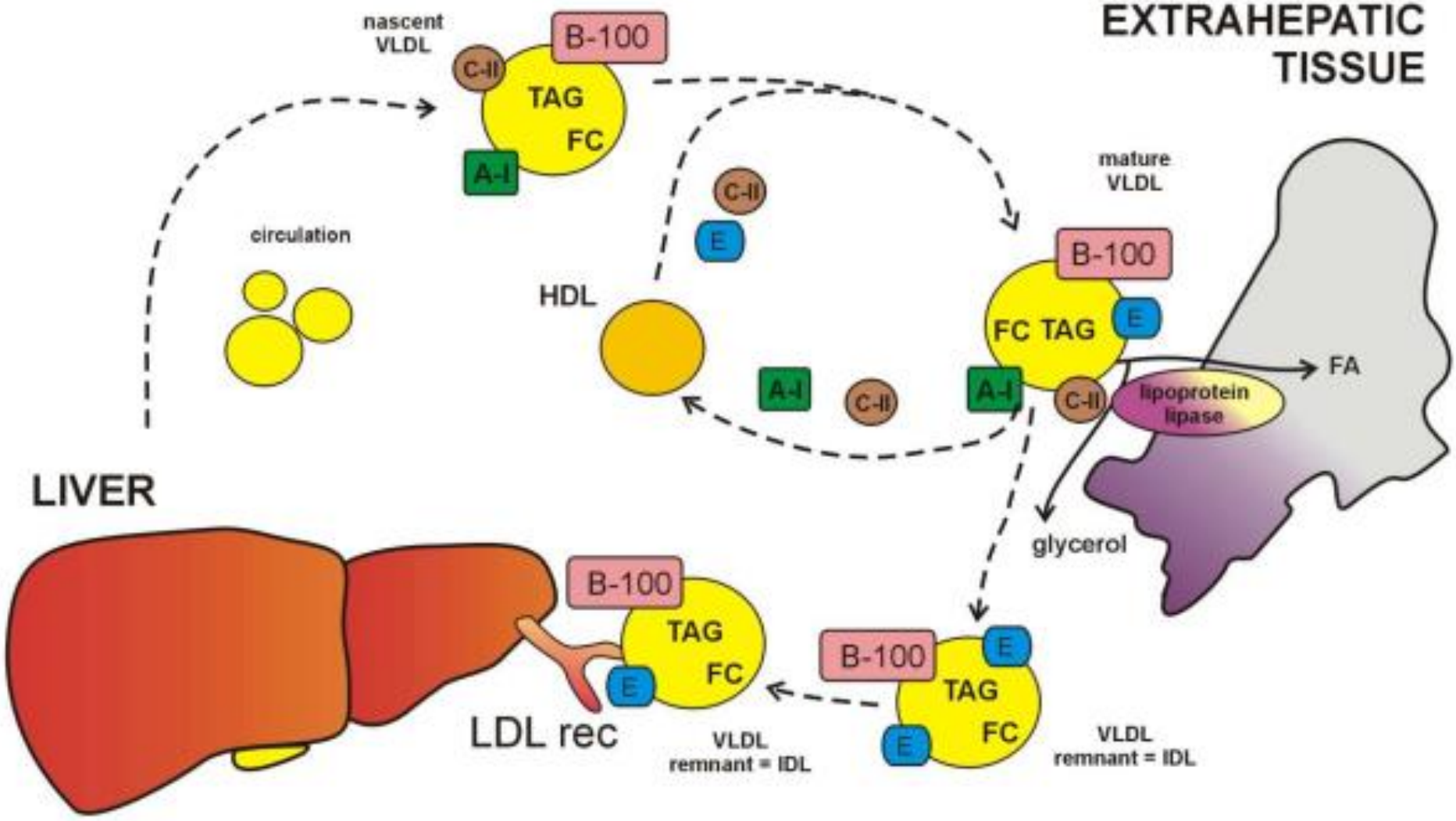


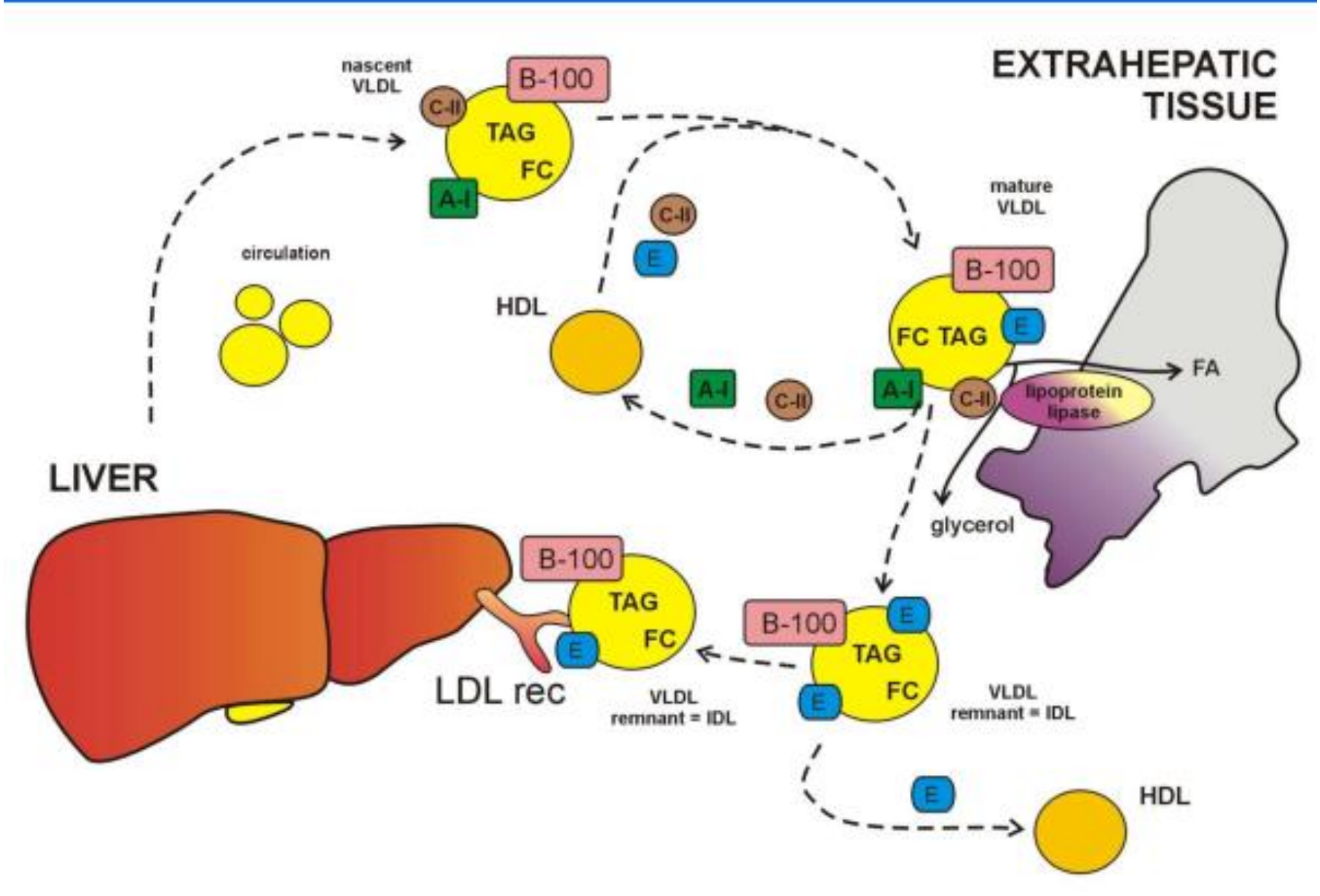
Fate of VLDLs



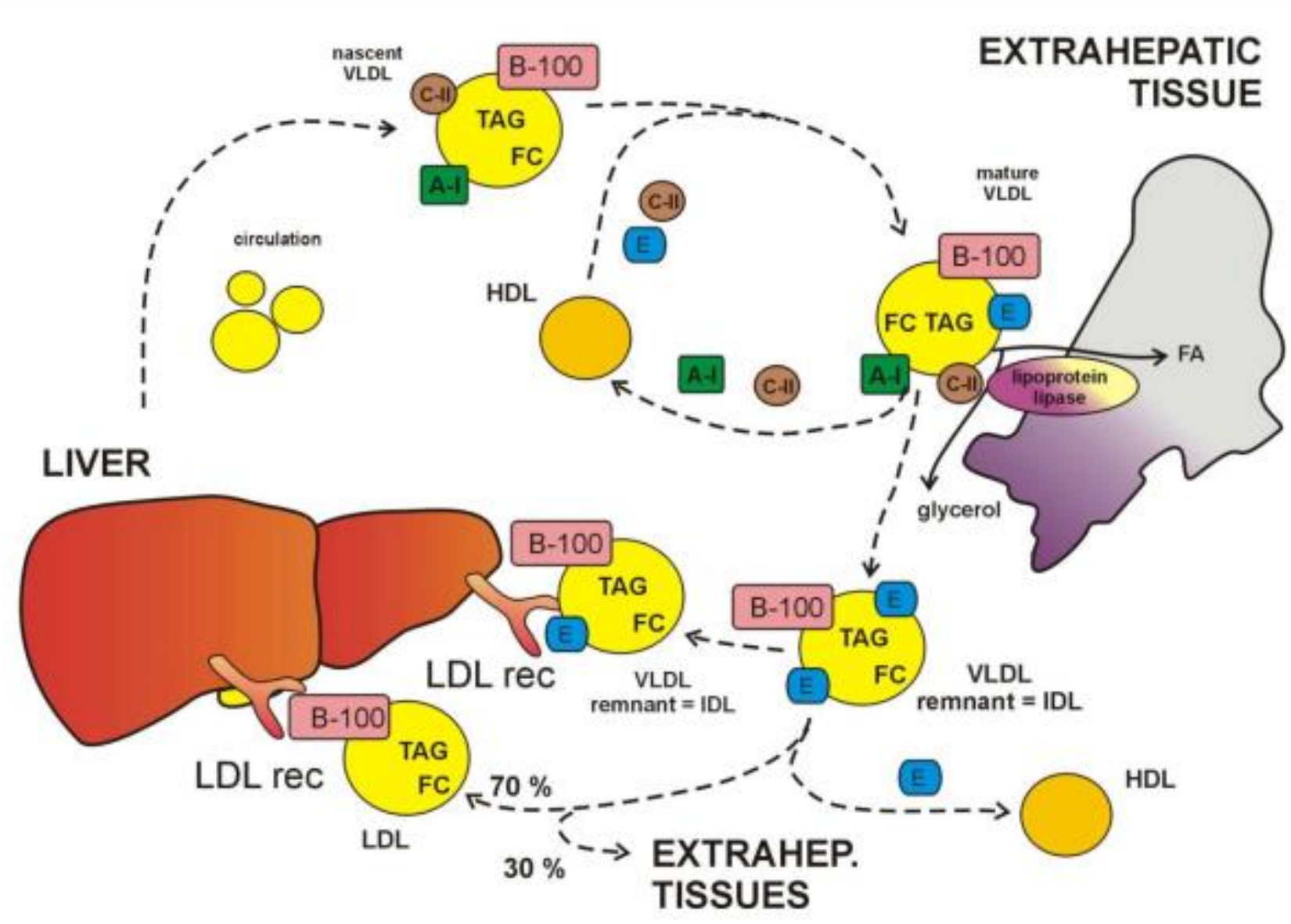
Fate of VLDLs



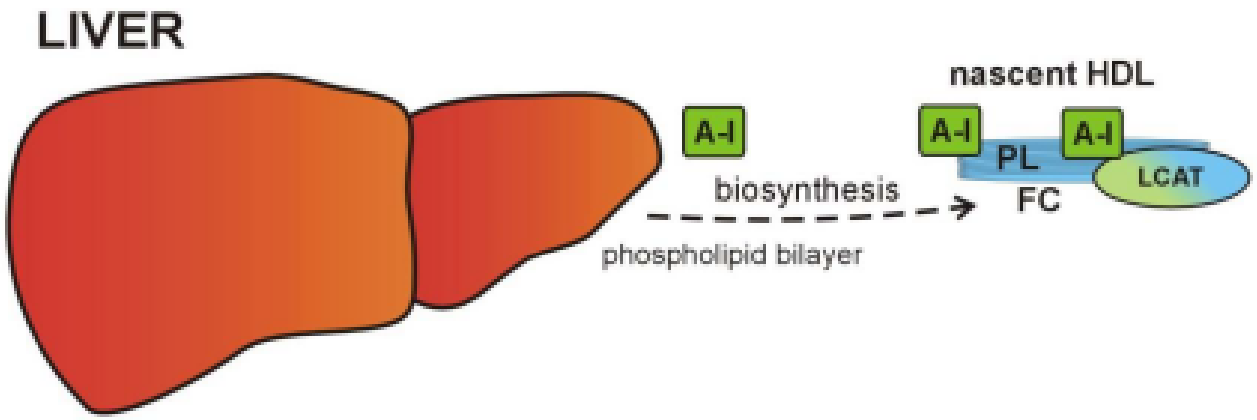
Fate of VLDLs



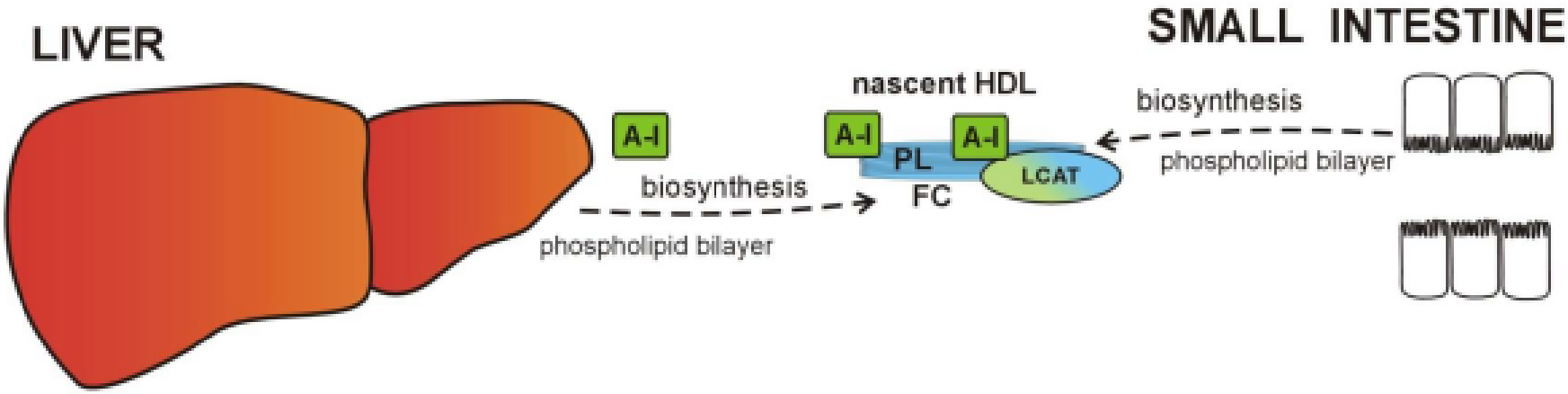
Fate of VLDLs



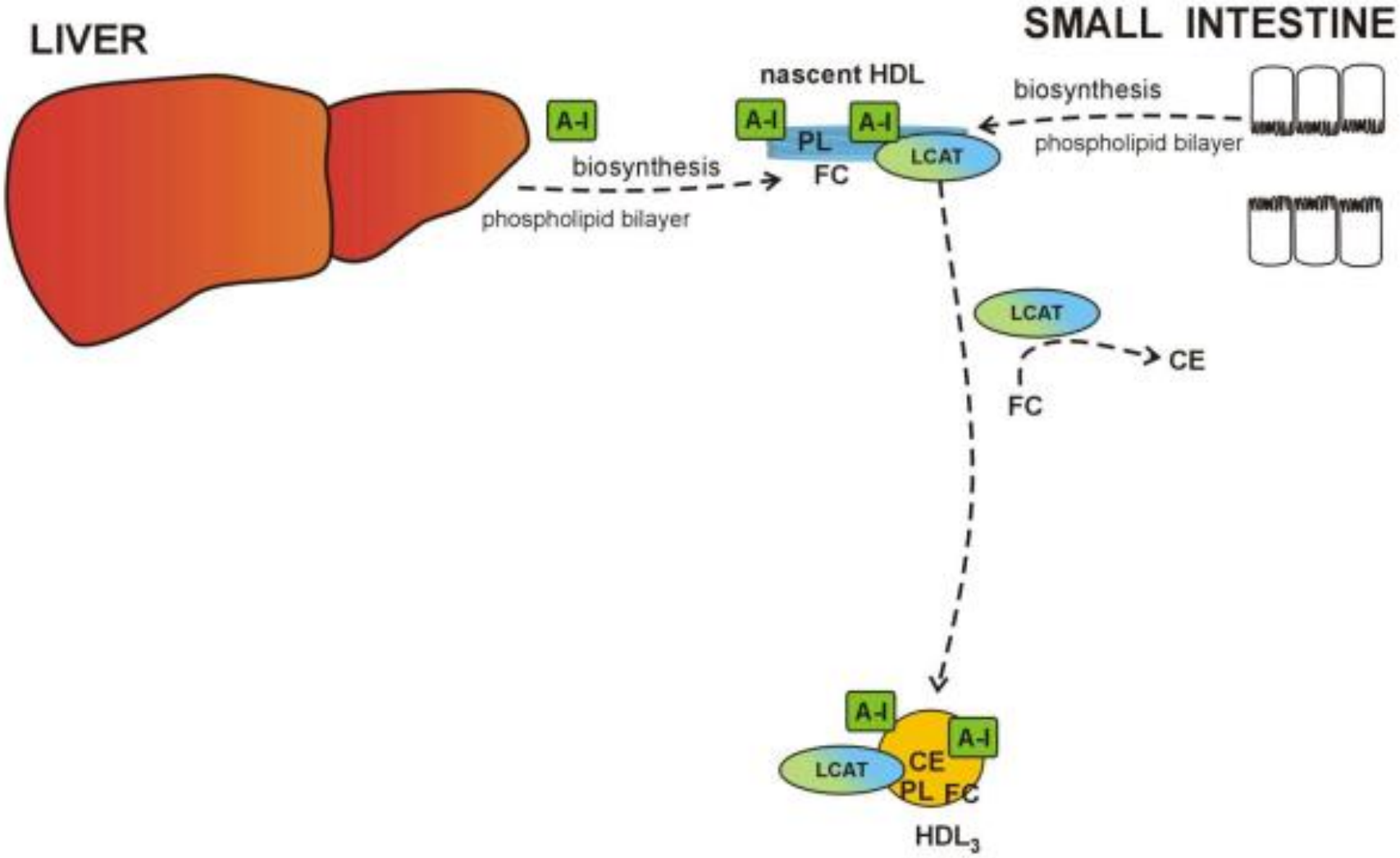
HDL and reverse cholesterol transport



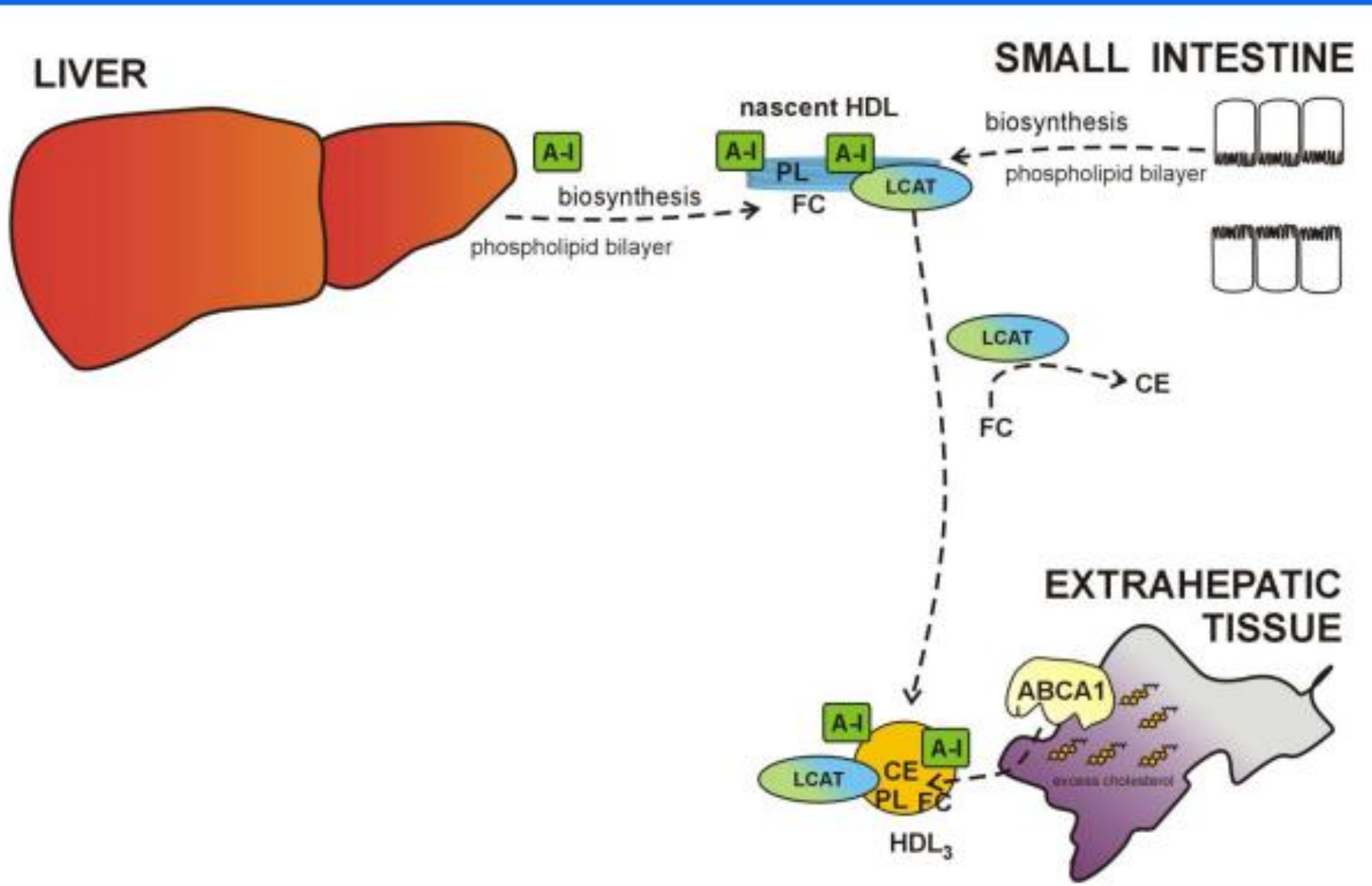
HDL and reverse cholesterol transport



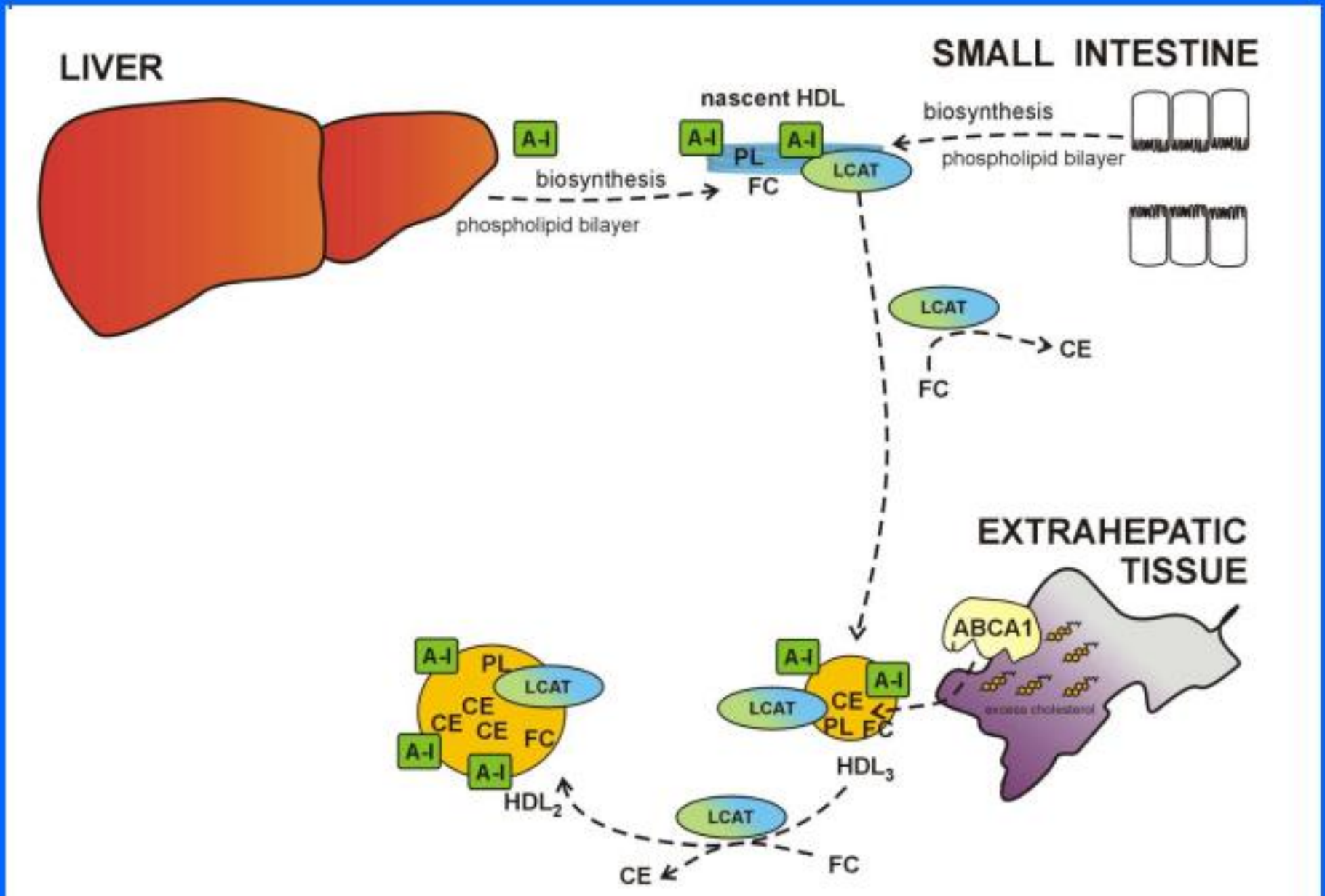
HDL and reverse cholesterol transport



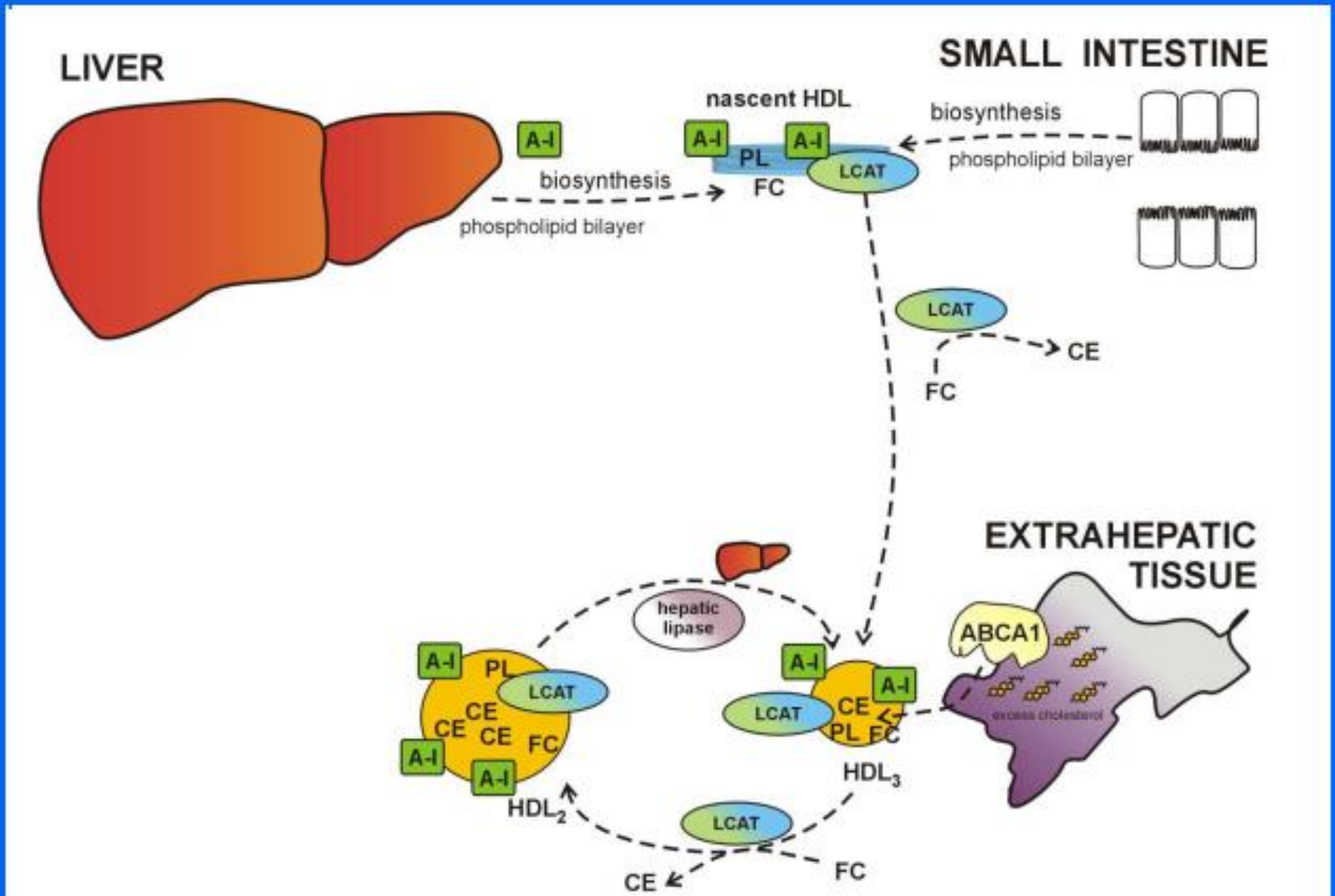
HDL and reverse cholesterol transport



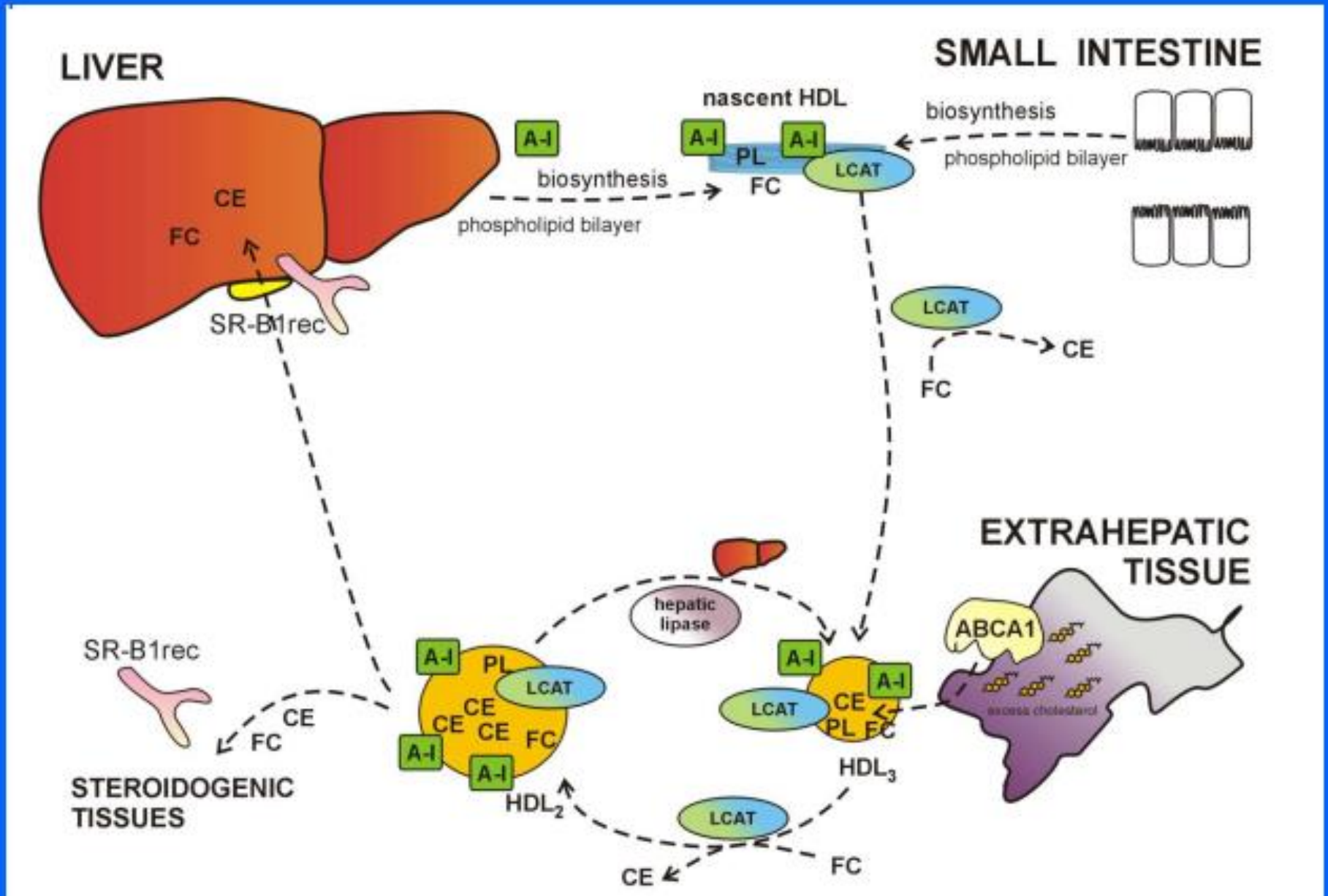
HDL and reverse cholesterol transport



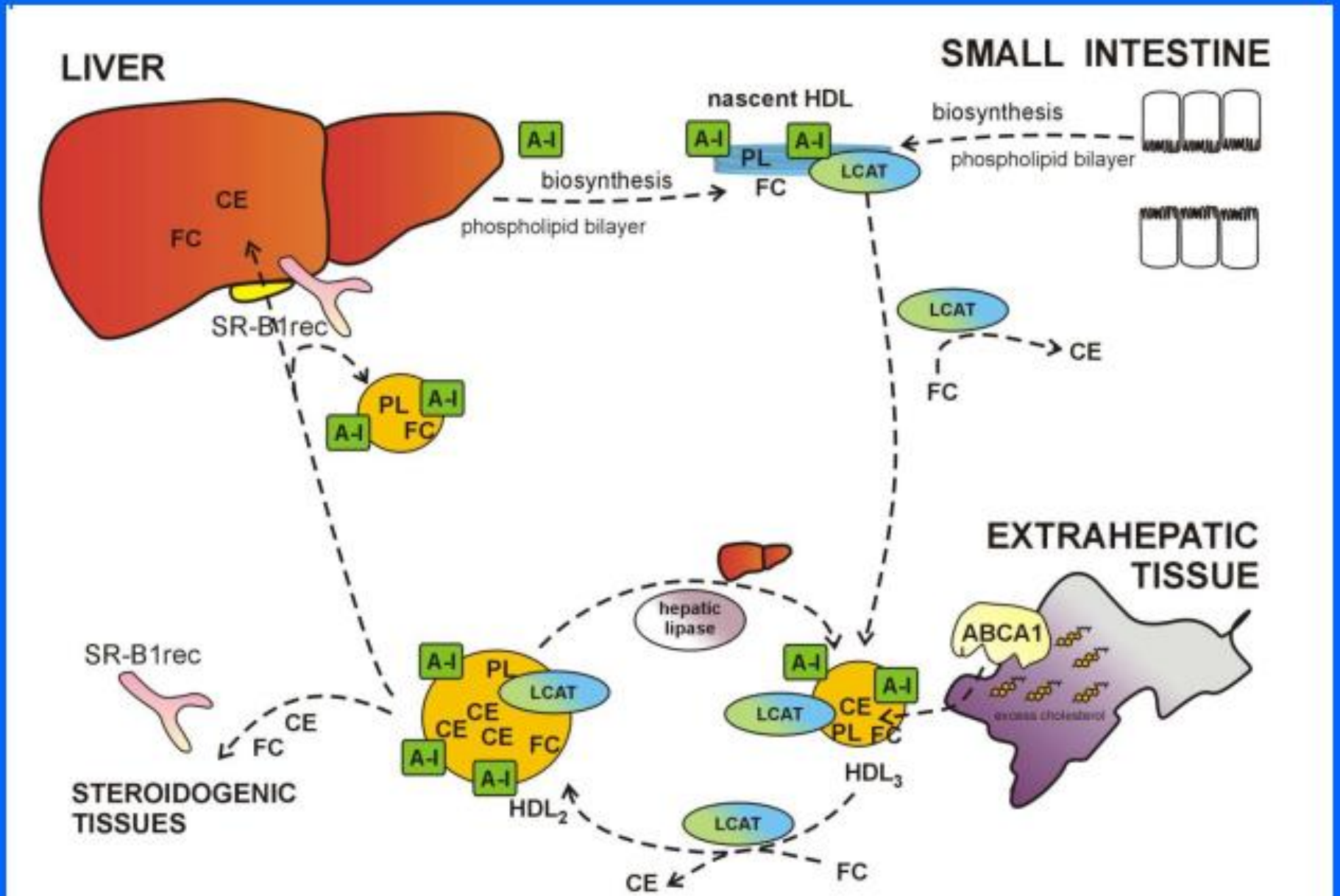
HDL and reverse cholesterol transport



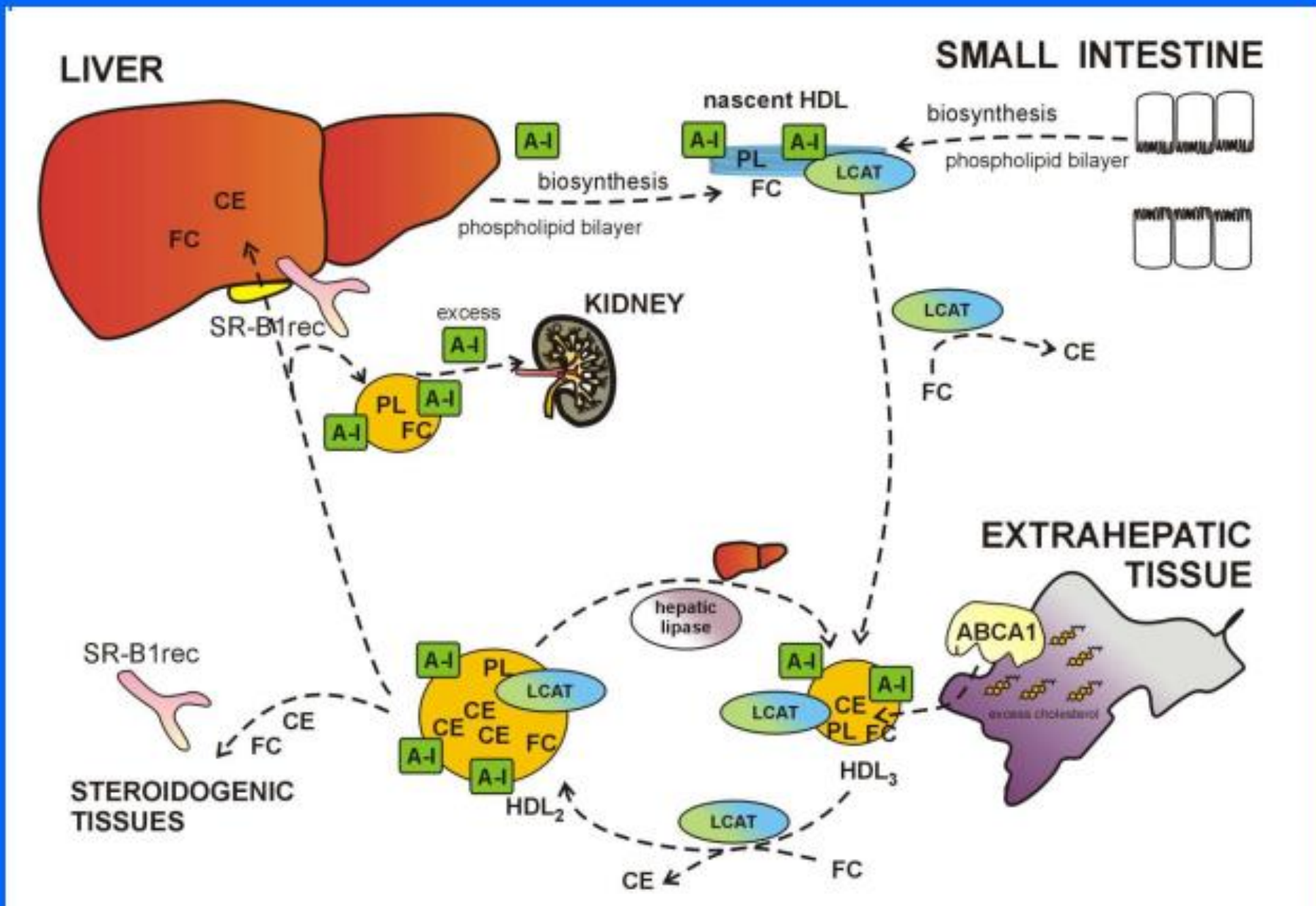
HDL and reverse cholesterol transport



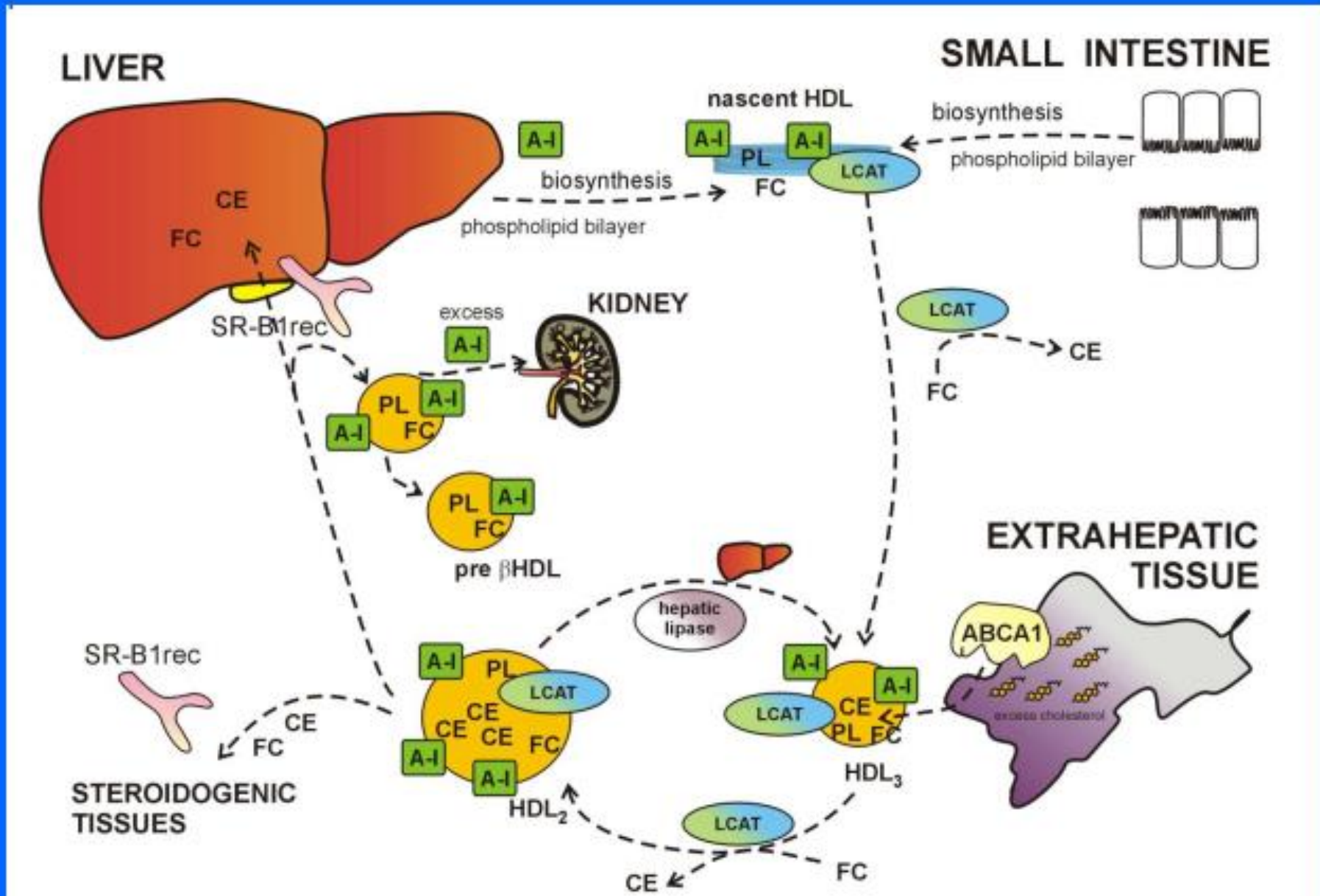
HDL and reverse cholesterol transport



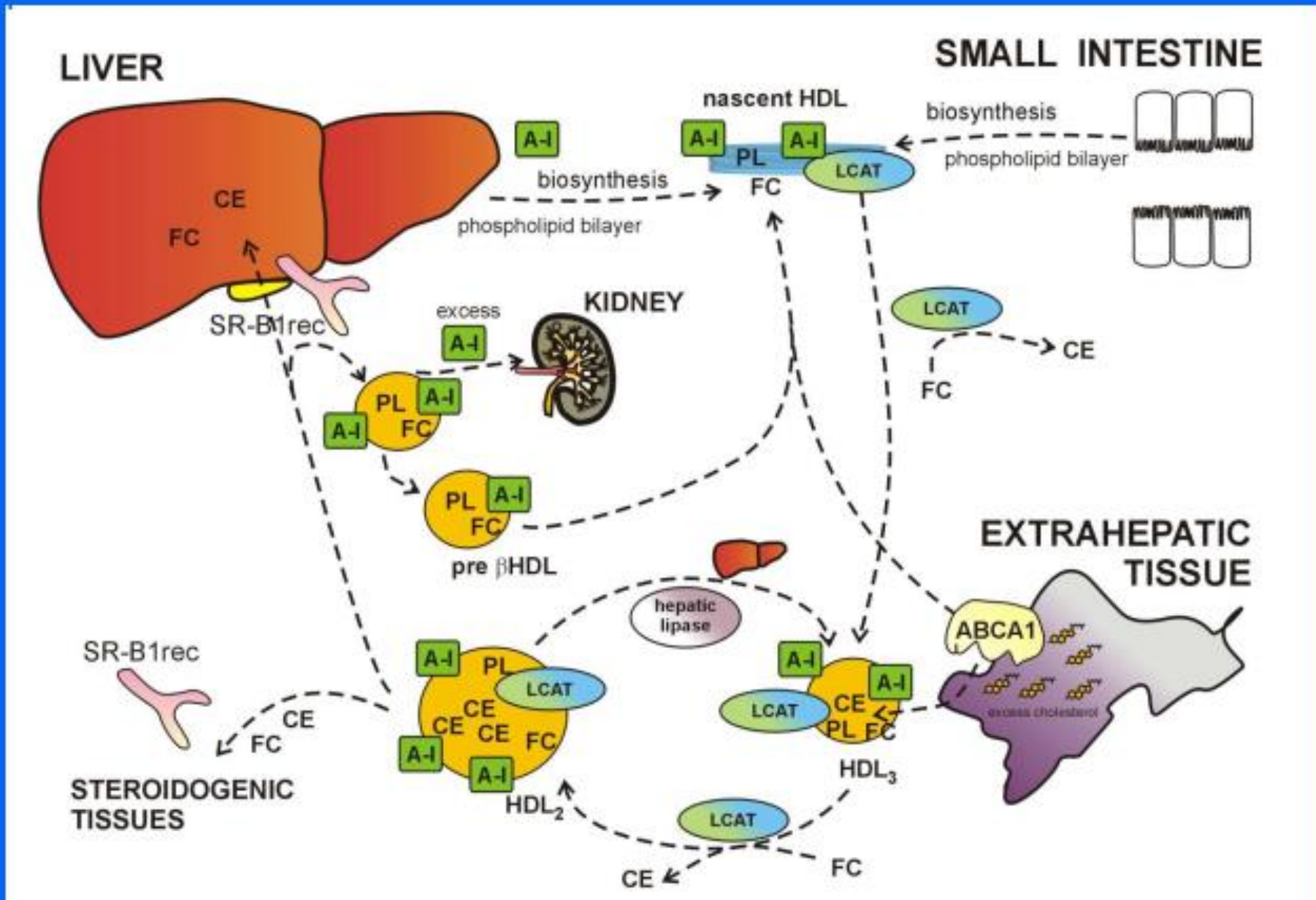
HDL and reverse cholesterol transport



HDL and reverse cholesterol transport

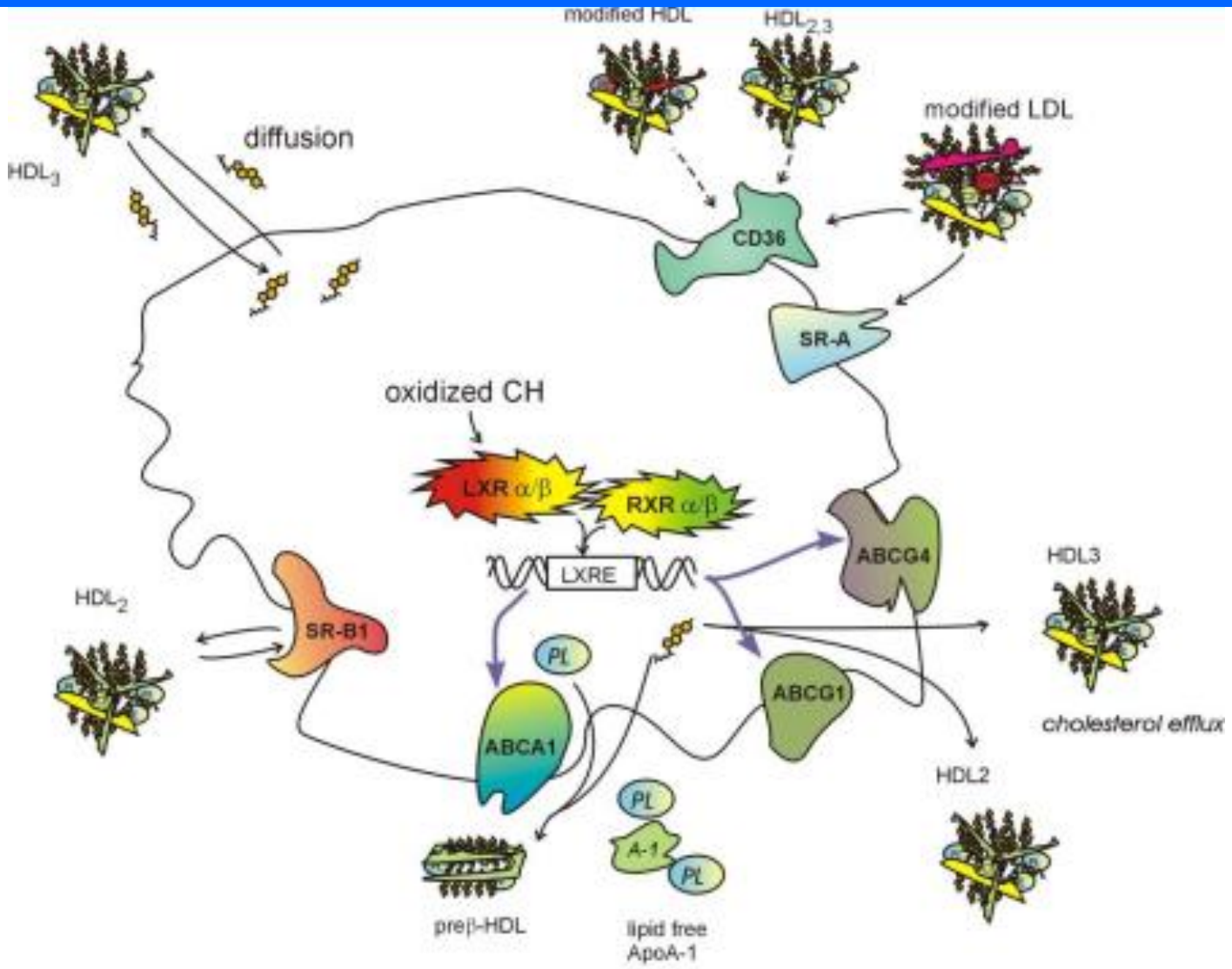


HDL and reverse cholesterol transport



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)

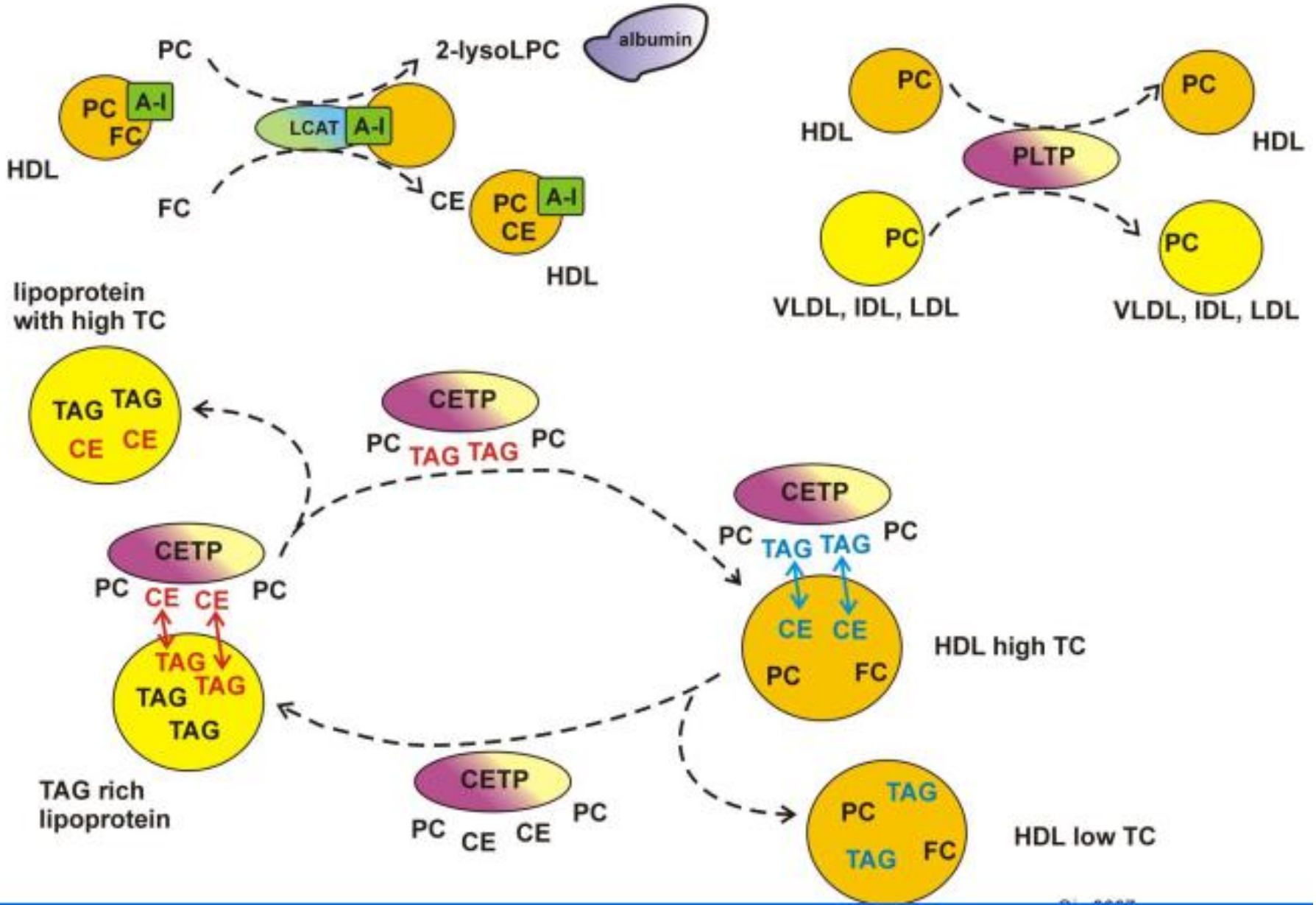
- liberation of oxidized FA from oxPL molecules (PON-1, PAF-AH)

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

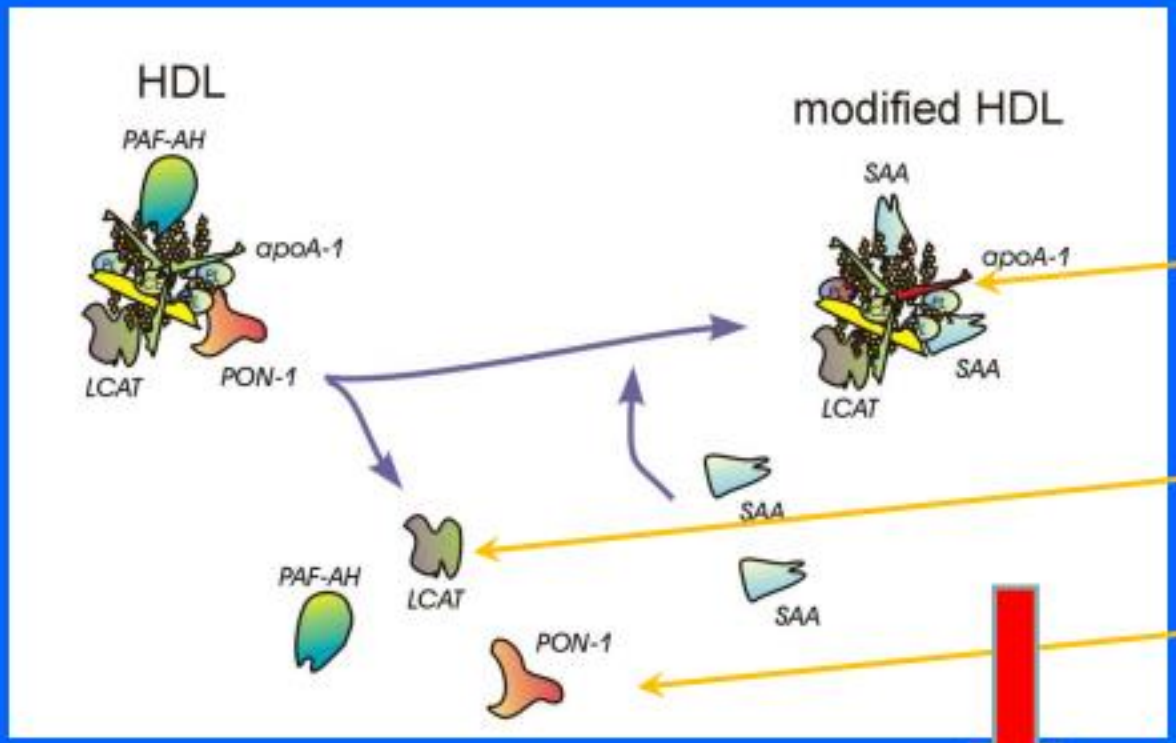
  platelet-activating factor acetylhydrolase (PAF-AH)

  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)

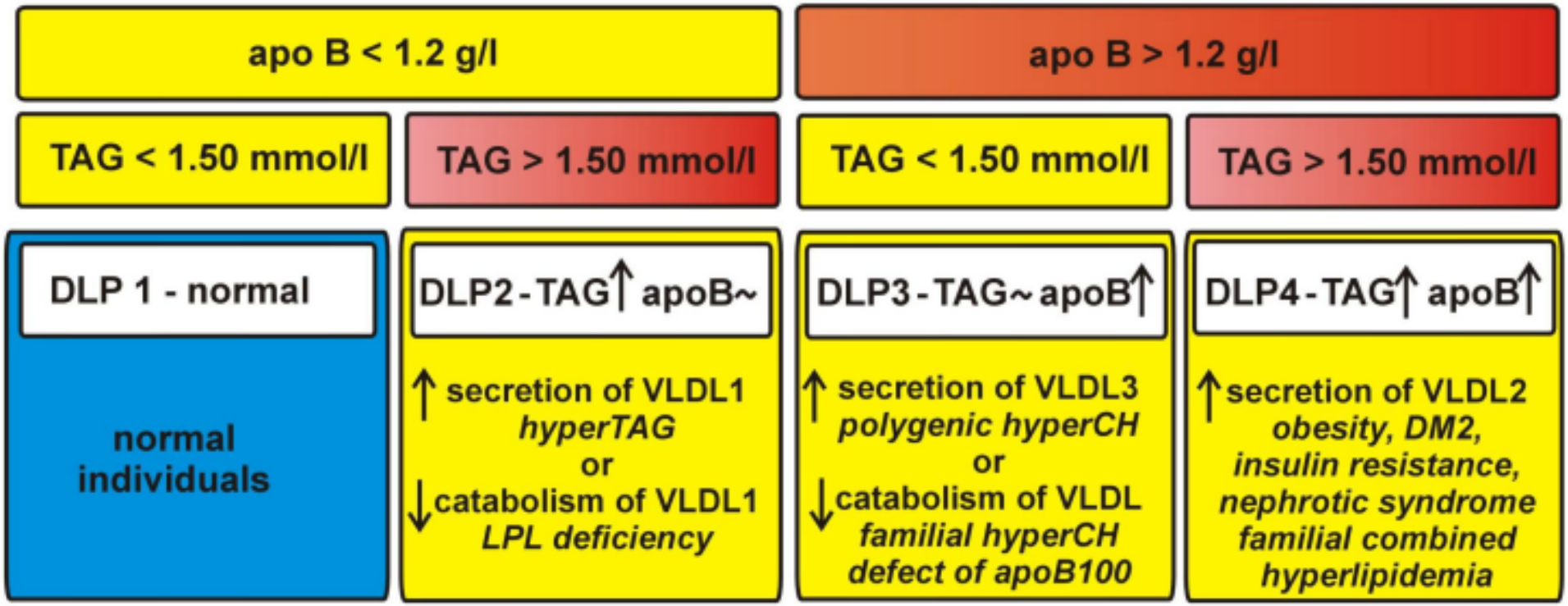
DM – diabetes mellitus

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

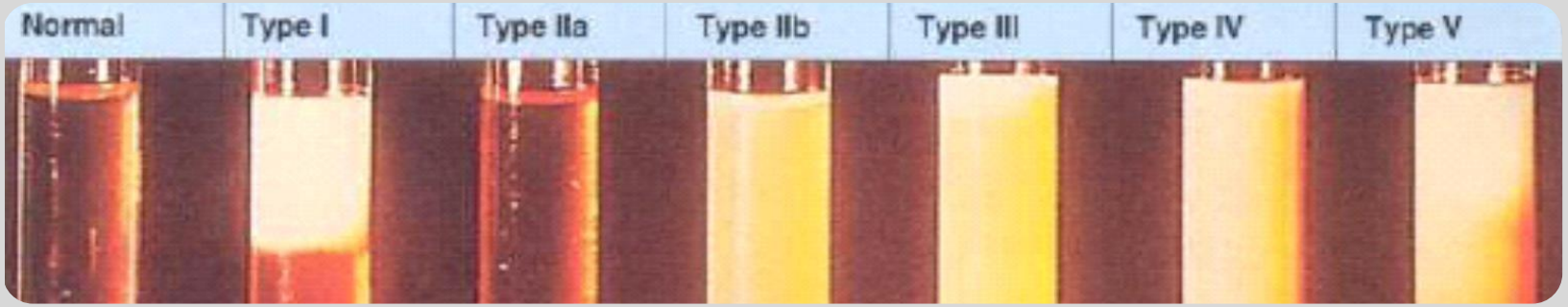
LDL – low density lipoproteins, VLDL – very low density lipoproteins, CM - chylomicrons, IDL – intermediary density lipoproteins, HLP - hyperlipoproteinemia

CLASSIFICATION OF DISTURBED LIPID METABOLISM by Sniderman



VLDL1, VLDL2, VLDL3 – subpopulations of VLDL particles

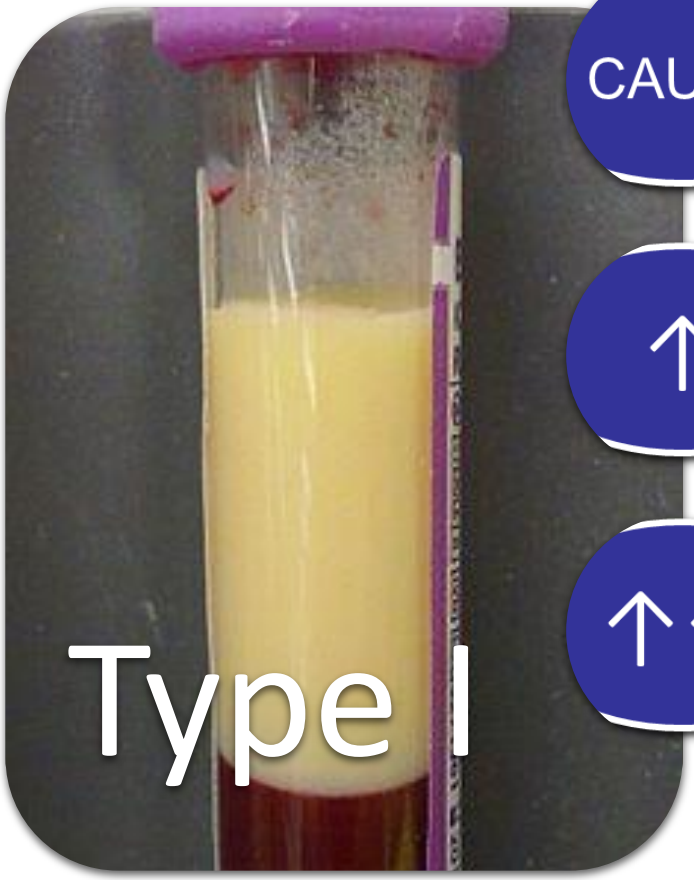
Hyperlipoproteinaemia



Fredrickson(WHO) classification

Fredrickson Classification	
Type I	High chylomicrons
Type II Type IIa Type IIb	 High LDL High LDL and VLDL
Type III	High chylomicrons and Intermediate Density Lipoprotein (IDL)
Type IV	High Triglycerides
Type V	Very similar to Type I, but with high VLDL
Non-classified forms: Hypo-alpha lipoproteinemia Hypo-beta lipoproteinemia	

Type I Hyperlipoproteinemia



CAUSE

Lipoprotein lipase deficency

↑

Chylomicron

↑↑

Triacylglycerol

Type IIa Hyperlipoproteinemia

Most common

Familial hypercholesterolemia

Defective LDL receptors

Plasma LDL & cholesterol level are elevated

Type IIb Hyperlipoproteinemia

Excess of apo-B

↑Pre-beta & beta (VLDL & LDL)

↑Total cholesterol, LDL, VLDL & TG

Type III Hyperlipoproteinemia

Abnormal apo-E

‘Broad beta' band (IDL)

↑Total cholesterol & TG

Type IV Hyperlipoproteinemia

Overproduction of VLDL

Pre-beta (VLDL)

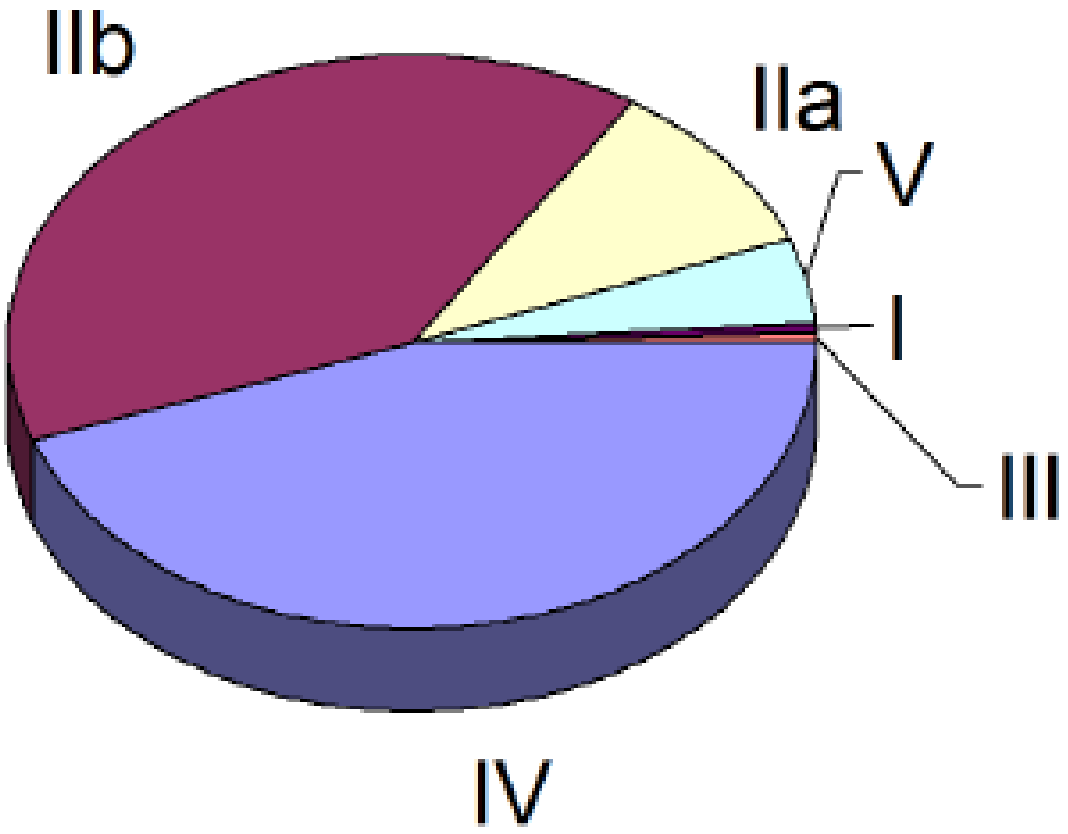
↑Triacylglycerol

Type V Hyperlipoproteinemia

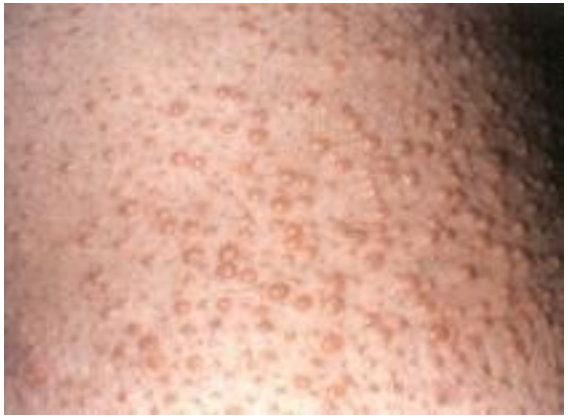
Secondary to other causes

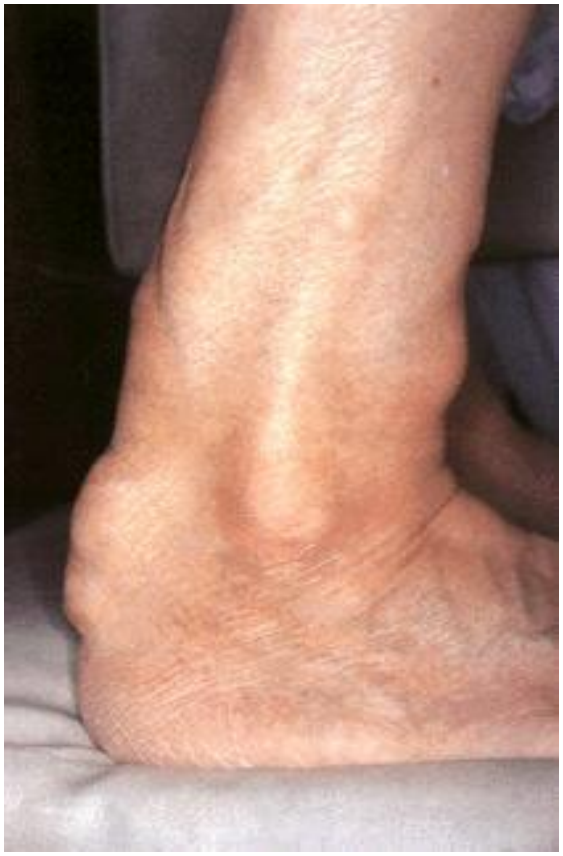
Pre-beta (VLDL) plus chylomicrons

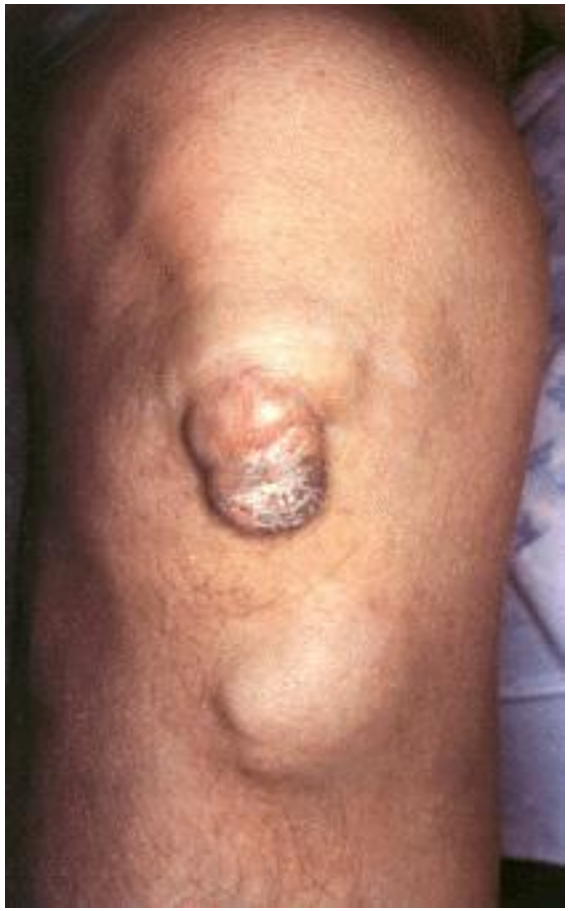
↑Total cholesterol & TG

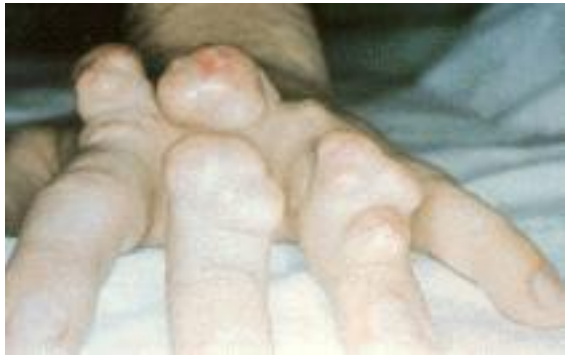


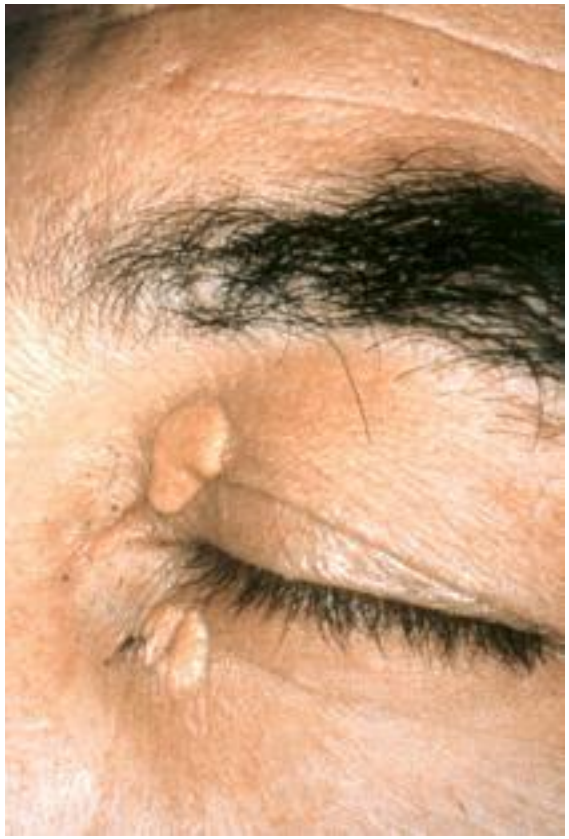
Relative prevalence of familial forms of hyperlipoproteinemia[20]

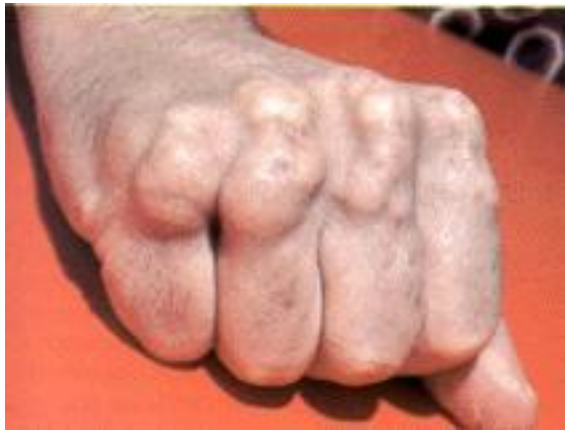












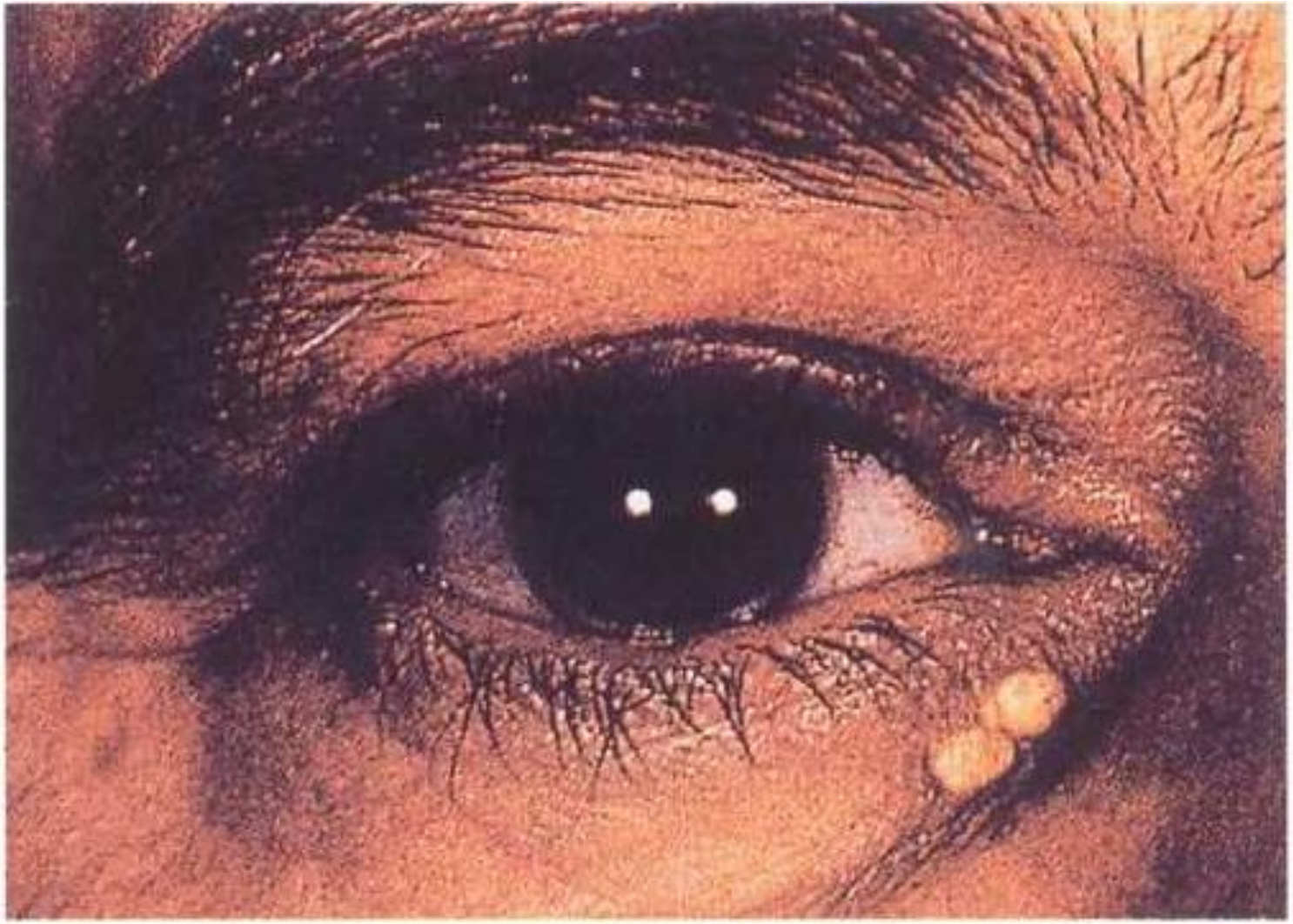
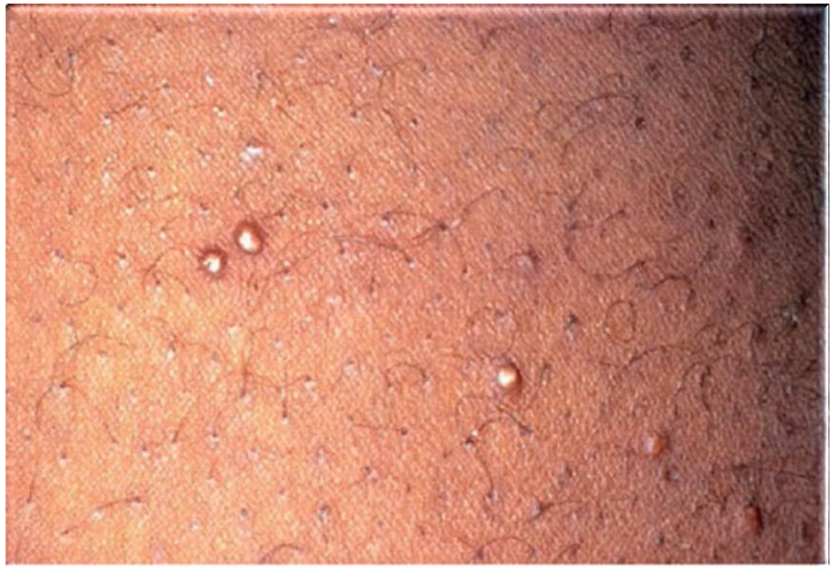


Fig. 1 **Xanthelasmas in younger individuals (age <40 years) usually indicate hypercholesterolaemia.** In the elderly they do not carry the same significance.



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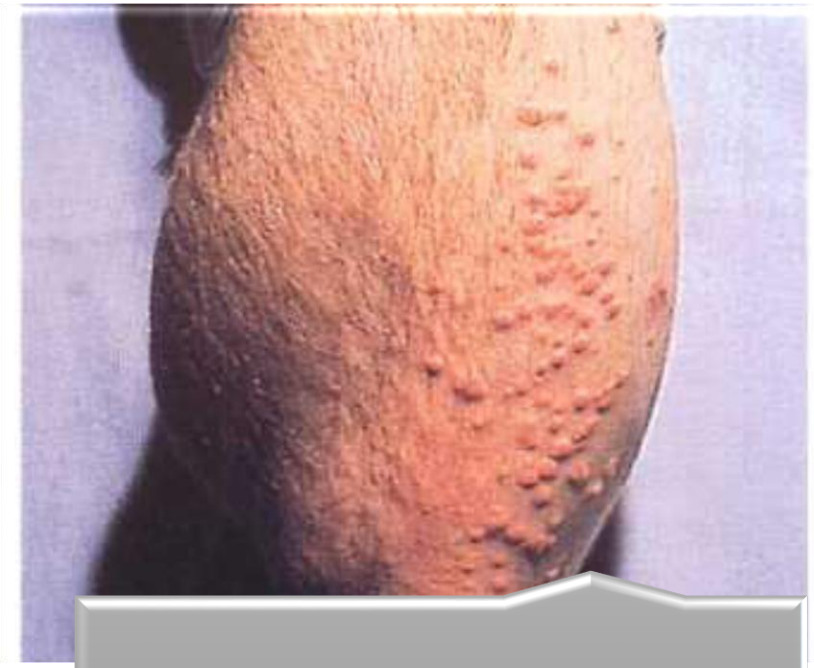
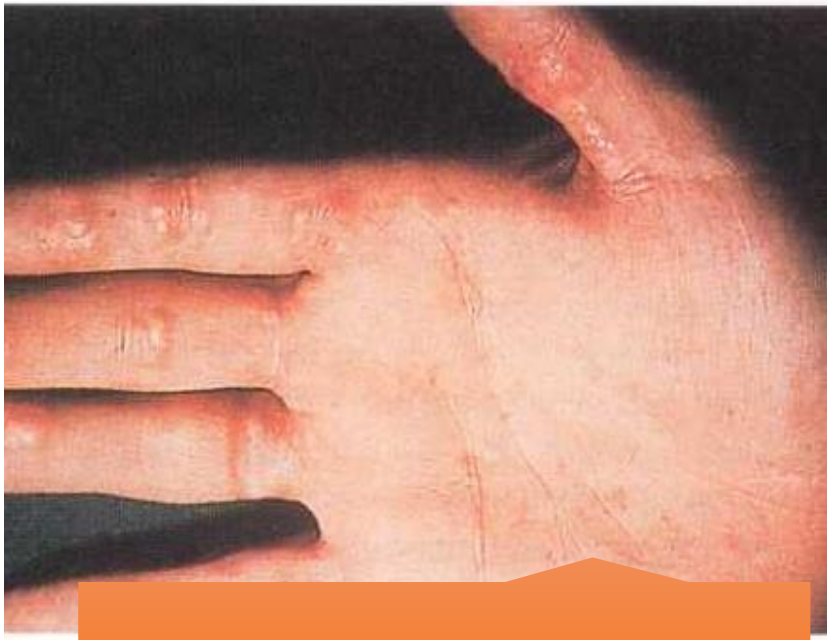
Eruptive xanthoma



Eruptive xanthoma



Palmar xanthoma

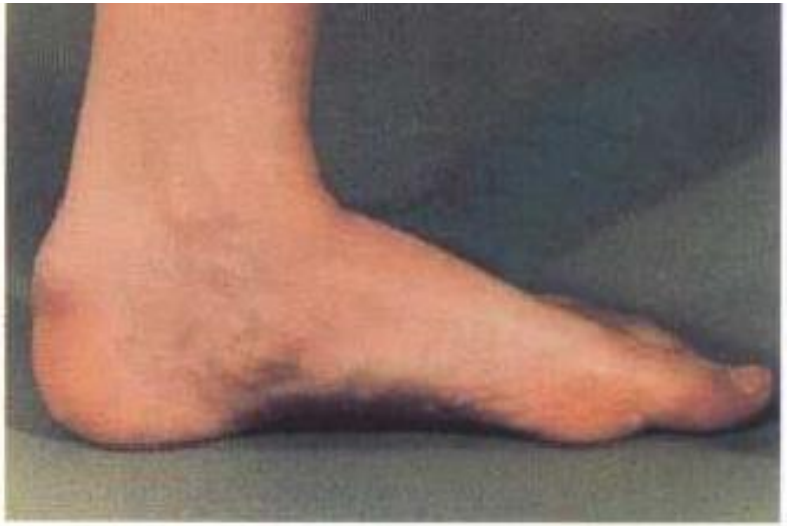


Fig. 5 **Tendon xanthomas.** These are pathognomic for fa

Tendon xanthoma

Hypolipoproteinemia

Abetalipoproteinemia- AR rare hereditary DMP, completely lacking lipoprotein particles containing ApoB (chylomicrons, VLDL), the overall level of CHOL and TAG are low, fat malabsorption, steatorrhoea, stunted growth later formed retinitis pigmentosa and cerebellar

Ataxia is typical acanthocytosis (stratum erythrocytes) deficit of fat-soluble vitamins, impaired cortisol lipids accumulate in the epithelium, gut - vakuoalizace, the body lacks essential MK (linoleic acid)

Analfalipoproteinemie (Tangier disease) decreased levels of HDL and ApoA-I, also lower LDL and total CHOL, HDL does not pass ApoCII → just VLDL, CHOL esters accumulation in tissues, yellowish enlarged tonsils, hepatosplenomegaly and corneal infiltration, higher incidence of the AT

Familial hypolipoproteinemia associated with longevity, probably for the low incidence of myocardial infarction. It is still considered a rare genetic, abnormality, probably with autosomal dominant inheritance. LDL cholesterol levels are reduced below 5 th percentile threshold normal range.

familial hypoalphalipoproteinemia

It is a genetic lipoprotein abnormalities associated with the occurrence of longevity in the family (about 8 to 12 years compared to the average in the population); expected form of inheritance is autosomal dominant. Familial forms, however, be distinguished from forms obtained (secondary) eg. when you abuse alcohol or use contraceptive preparations or preparations based estrogens. The syndrome is characterized by significant increasing the HDL cholesterol-1 lipoprotein to ELFO), mild to moderate increase celkového (increased cholesterol in plasma and normal concentrations of S-triglycerides. Are multiplied HDL particles containing only ApoAI not containing particles as ApoAI and ApoAII

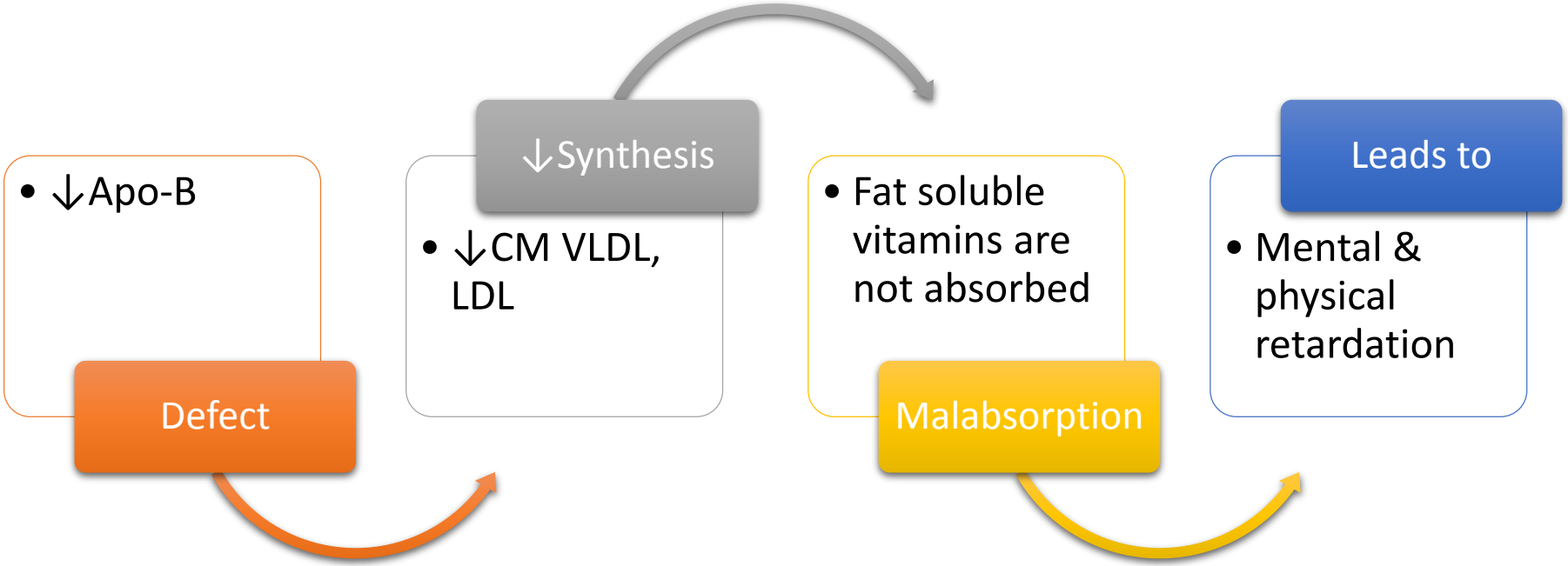
[LPA I And II]. Abnormality is probably due to increased synthesis of apo AI. There is a reduced risk of cardiovascular disease

induced atherosclerosis.

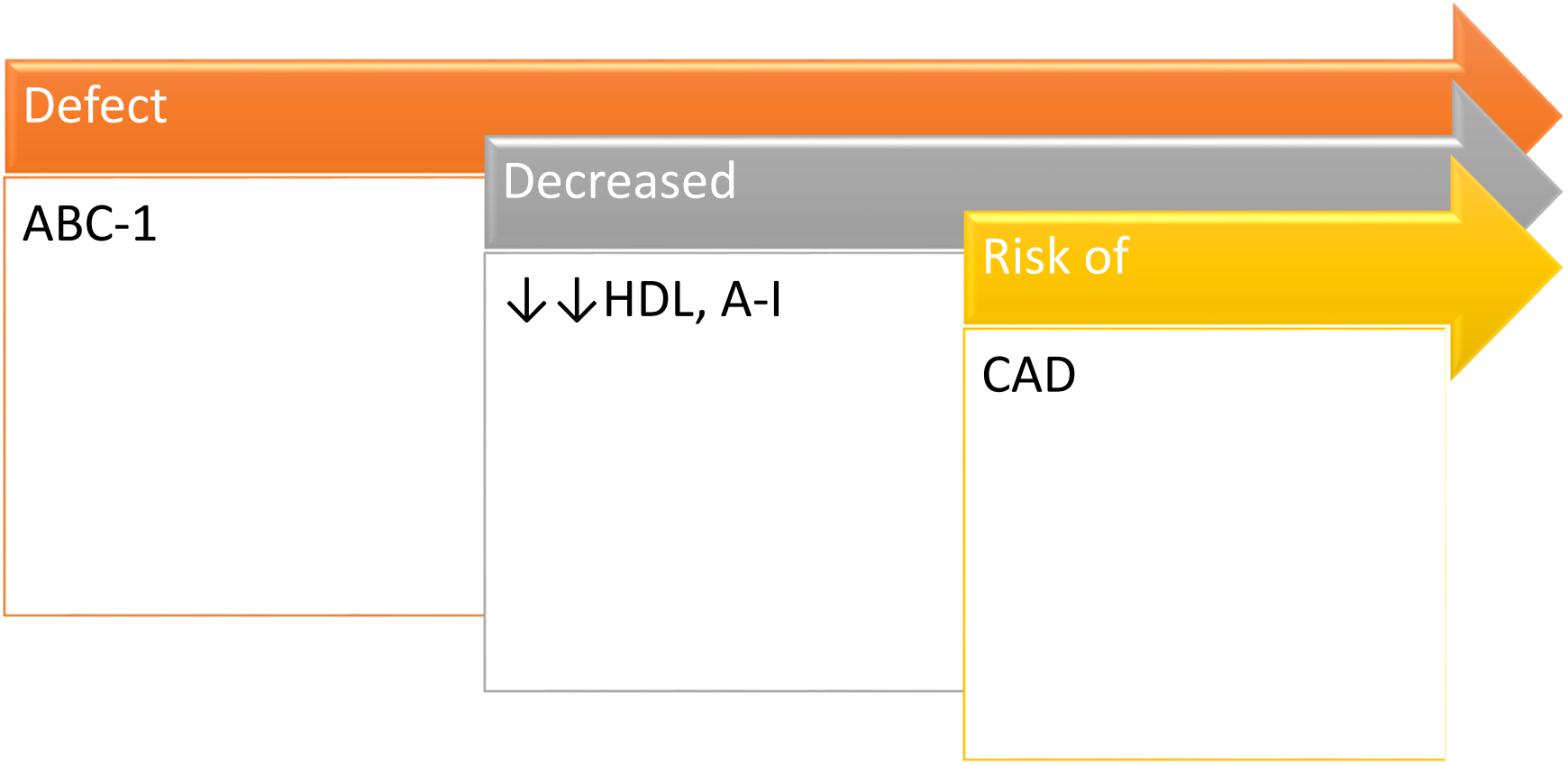
Hypolipoproteinemia

Abetalipoproteinemia	Familial lipoprotein deficiency[Tangier disease]
• Defect in synthesis of apo-B	• Defect in synthesis of apo-A

Abetalipoproteinemia



Familial α-lipoprotein deficiency[Tangier disease]



Storage disorders cholesterol

Wolman disease – rare AR deposition of cholesterol esters and triacylglycerols in the liver cells, kidney, adrenals, hematopoietic system and thin intestines. It is caused by the lack of lysosomal acid lipase., Accumulation of cholesterol esters in lysosomes of cells of the affected tissues hepatosplenomegaly, repeated vomiting, persistent diarrhea with steatorrhoea, bilateral adrenal calcification. fatal.

Familiar deficit of lecithin: cholesterol acyltransferase (LCAT)

It goes into making the deficit a key enzyme in cholesterol esterification. AR levels are elevated triglycerides and the level of cholesterol is variable; but lacking cholesterol esters (3-30% vs. 75-70%). Leads to lipid deposition in the cornea (opalescent) in glomerular membrane (proteinuria) in bone marrow and spleen (Sea Blue histiocytes) in erythrocytes (anemia) in the vascular wall (atheromas). They are changes in the plasma lipoproteins: triacylglycerolemie 2, 26-11, 3 mmol / l. Most classes have abnormal lipoprotein
character

Sphingolipidoses inborn errors of metabolism of membrane lipids (sphingolipids) - the accumulation of these lipids in the relevant bodies.

Gangliosidosis - Norman-Landigova disease –mental retardation, degeneration of the nervous system, Tay-Sachs gangliosido- Gaucher disease, Scholzová disease, mental retardation, degeneration of the central and peripheral nervous system-Fabry disease

Gaucher disease - defect lyzosomové B glucozocerebrosidase, glukózocerebrosid accumulate in the spleen, liver and bone marrow

Niemanova and Pick disease –stogage sphingomyelin and cholesterol

Disorders of β-oxidation of fatty acids

beta-oxidation contributes significantly to ensuring the energy needs in a period of fasting; it is a direct source of energy for heart and muscle
tissue and source of ketone bodies for about 20 CNSje known disorders are the most common AR inherited disorder include MCAD (Medium-Chain-acyl
CoA dehydrogenase) and LCHAD (Long Chain 3-OH-acyl-CoA dehydrogenase)

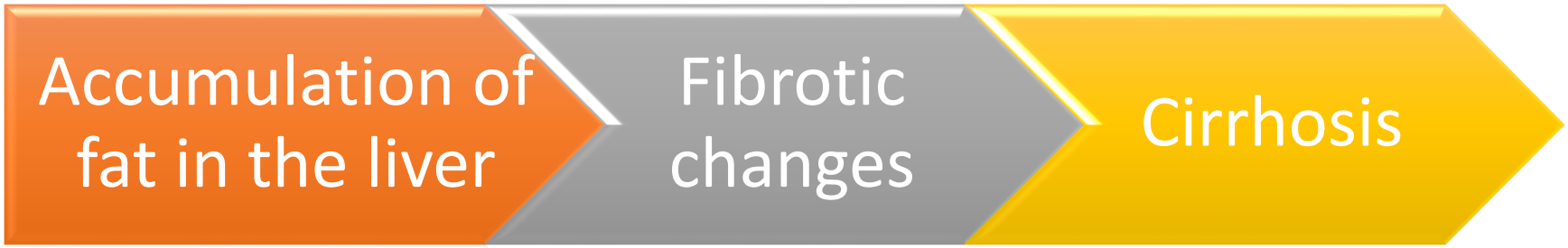
Fatty liver

Excessive accumulation of fat in the liver parenchymal cells

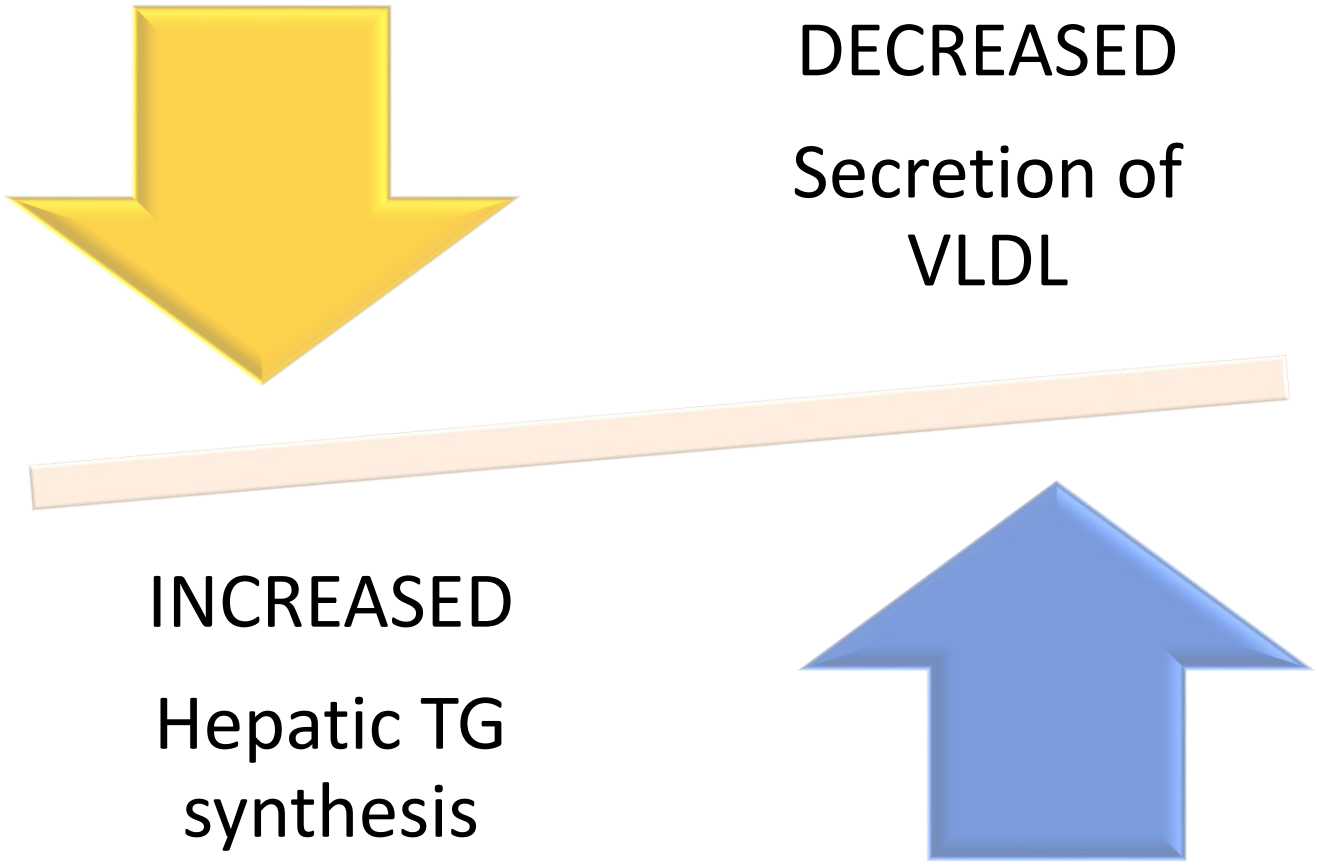
Liver is not a storage organ for fat

Liver contains about 5% fat

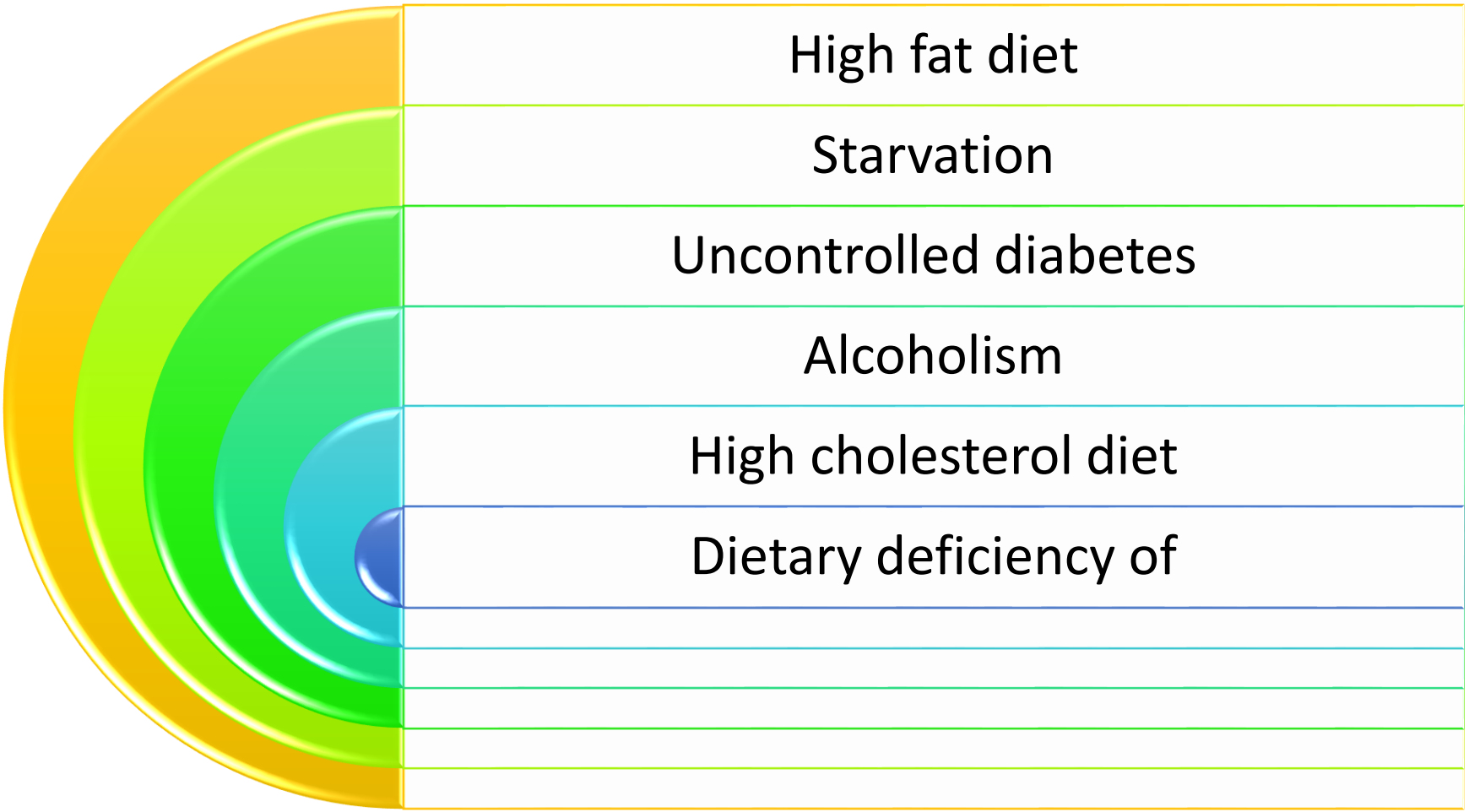
Fatty liver


Accumulation of fat in the liver
Fibrotic changes
Cirrhosis

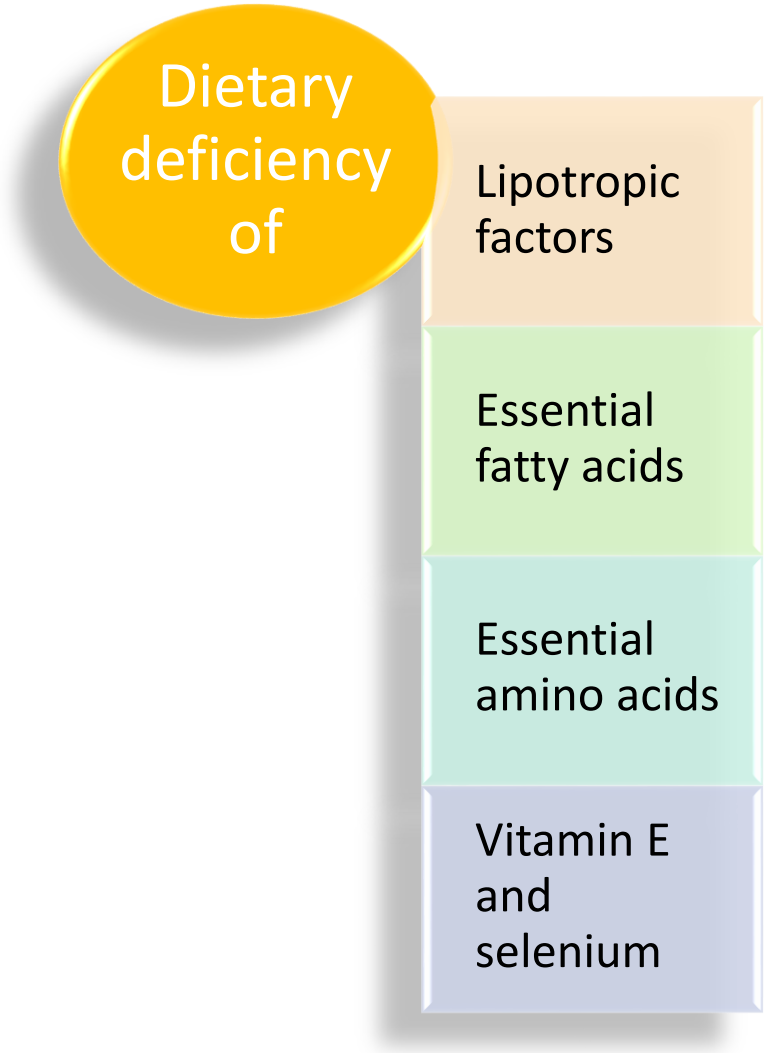
FATTY LIVER: CAUSES



Conditions that cause FATTY LIVER



Conditions that cause FATTY LIVER



LIPOTROPIC FACTORS

Substances that prevent the accumulation of fat in the liver

- Choline
- Methionine
- Betain
- Vitamin B_{12}
- Folic acid

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

TCA cycle intermediates (oxaloacetate) are used for gluconeogenesis

acetylCoA excess

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

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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

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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

Regulation of the balance between lipid storage and mobilization in adipocytes

- the balance (ratio between lipogenesis and lipolysis) is a product of continuous neurohumoral regulation reflecting feeding/fasting cycling and immediate
- energy requirements of the body
- □ (a) normal adipocytes in a fed
- (postprandial) state
- – glucose is taken up by adipocytes via
- GLUT4 stimulated by insulin
- – FFA are released from TAG rich
- lipoproteins (mainly chylomicrons) by the
- action of LPL stimulated by insulin
- – surplus of glucose is the main source for
- TAG production
- □ (b) normal adipocytes in a fasted state