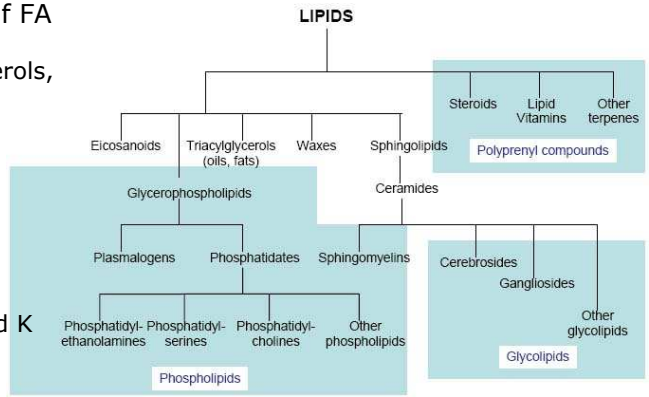
# Lipid metabolism disorders



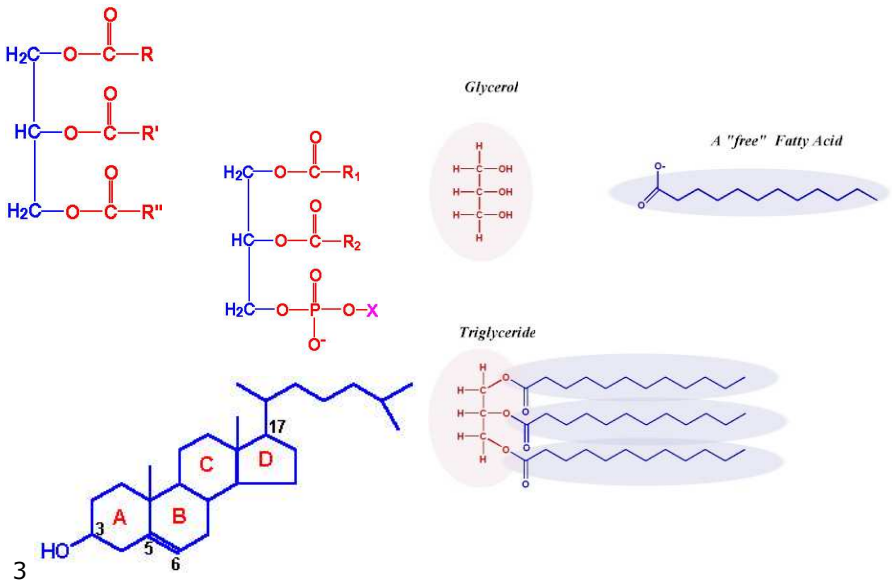
# Lipids

- any fat-soluble (= lipophilic) molecule
  - fats (TAG, oils)
  - fatty acids (FA)
  - derivatives of FA
    - mono-, diacylglycerols, ..
  - eikosanoids
  - waxes
  - cholesterol
  - sterols
  - fat-soluble vitamins
    - A, D, E and K





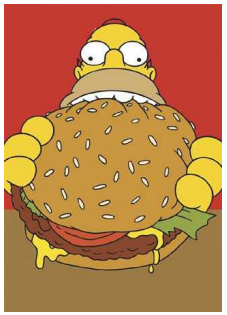

# Lipids – TAG/FFA, PL, CH





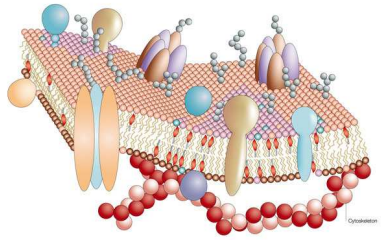

# Physiologic importance of lipids

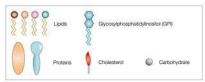
- lipids are
  - (1) source of energy (TAG → FFA) – typical daily intake ~80-100 g/d
    - adipose tissue (containing TAG) represents ~1/5 body weight in lean subject and thus ~570 000 kJ energy store (that's enough for ~3 month complete starving)
  - (2) building material for the synthesis of many compounds (CH) - typical daily intake ~200-500 mg/d
    - signalling molecules (steroid hormones, vit. D, prostaglandins, enzyme cofactors)
    - components of plasma membranes (phospholipids and CH)
    - bile acids
- lipids:
  - triacylglycerols (TAG)
  - phospholipids (PL)
  - free cholesterol (CH) and cholesterol esters (CHE)
  - free fatty acids (FFA)
- concentration of lipids in the cells and lipoproteins in plasma is a result of an interaction between genetic factors and environment
- disorders
  - (1) metabolism of individual lipids
    - Tangier disease, Tay-Sachs, Niemann-Pick, …
  - (2) hyperlipoproteinemia (HLP)/dyslipidemia (DLP)
    - group of metabolic diseases characterised by increased/ decreased levels of certain lipids and lipoproteins in plasma due to:
      - their increased synthesis
      - decreased catabolism
      - event. decreased synthesis (HDL)
    - some disorders are atherogenic, Alzheimer disease association, …
- ☝increased plasma level of atherogenic lipoproteins needn't to be related to the amount of subcutaneous fat!!!!!
  - **HLP ≠ obesity!**

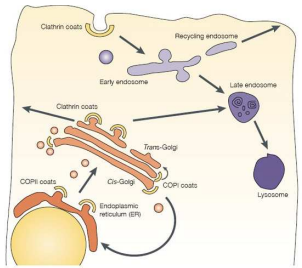


# Membrane lipids

- Important for
  - cellular compartmentalisation
    - organels, vesicules, …
  - membrane rigidity, i.e. permeability
    - ions – polarity, apoptosis, regulation, …
  - signal transduction
    - tyrosin kinases association, G-protein coupled receptors, …
  - membrane trafficking
    - endocytosis, secretion, …
  - lateral membrane inhomogeneity (microdomains, lipid rafts)
  - regulation of lipid metabolism
    - SREBP, LXR/RXR, …



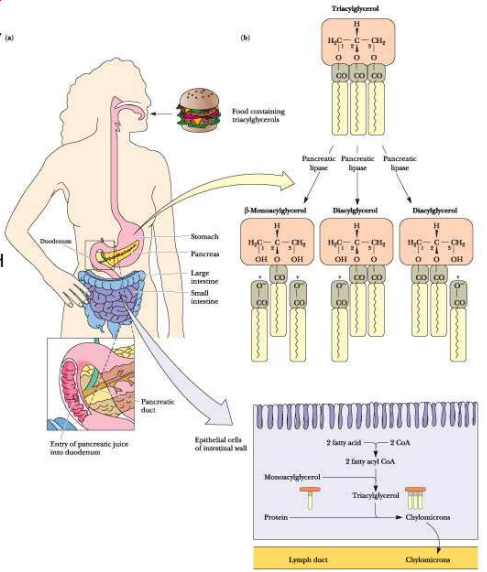





# Lipid digestion and absorption

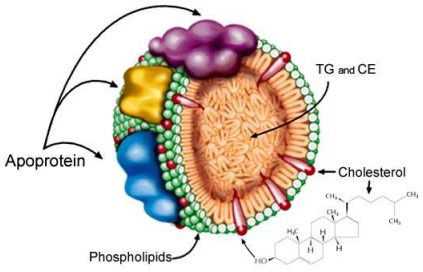
- water-insoluble lipids in foods (TAG, CH, PL) are mechanically (by GIT movements) and chemically (by bile) emulgated so that they are accessible to the enzymes
  - TAG are digested by pancreatic lipase in intestine to FFA, monoacylglycerols and diacylglycerols
  - PL are digested by pancreatic phospholipases
  - CHE are digested by pancreatic cholesterylester hydrolase to free CH
    - incomplete absorption from gut (~30-60%)
- lipids together with bile acids, lipid-soluble vitamins and other compounds form "mixed micels", which are absorbed by enterocytes
- enterocytes carry out re-esterification of to TAG, synthesise apolipoproteins which they add to TAG and CH and thus form chylomicrons
- chylomicrons are released from enterocytes into lymph and subsequently blood

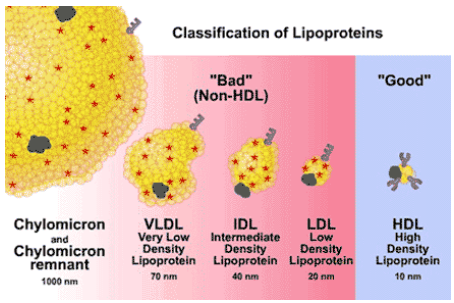





# Lipoproteins

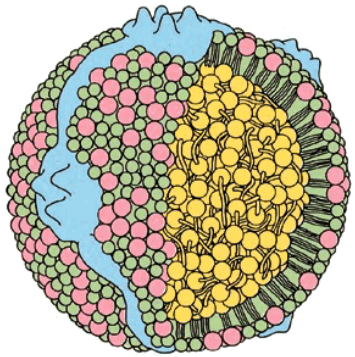
- lipoproteins = macromolecular complexes (particles) consisting of:
  - proteins (apolipoproteins, enzymes)
    - structural integrity, binding to receptors, exchange of lipids
  - lipids (CH, CHE, TAG, PL)
    - outer layer – PL, CH
    - inner core – CHE, TAG
- circulating lipoproteins
  - (1) intestine-derived
    - chylomicrons
  - (2) liver-derived
    - VLDL (very low density lipoproteins)
    - IDL (intermediate density lipoproteins)
    - LDL (low density lipoproteins)
    - HDL (high density lipoproteins)
  - (3) assembled in circulation
    - Lp(a) - from LDL and apo-a (liver)
- composition (lipids and apoPs) differ between particular lipoproteins
  - chylomicrons and VLDL are TAG-rich particles (TAG>>>>CH)
  - LDL and HDL carries CH>>>>TAG
- different lipoproteins have different metabolic fate
- plasma normally contains
  - <1% of chylomicrons
  - <10% of VLDLs
  - the rest is LDL and HDL






# Example - LDL

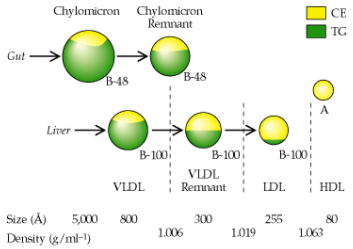


Unesterified cholesterol
Phospholipid
Cholesteryl ester
Protein B-100

# Apolipoproteins

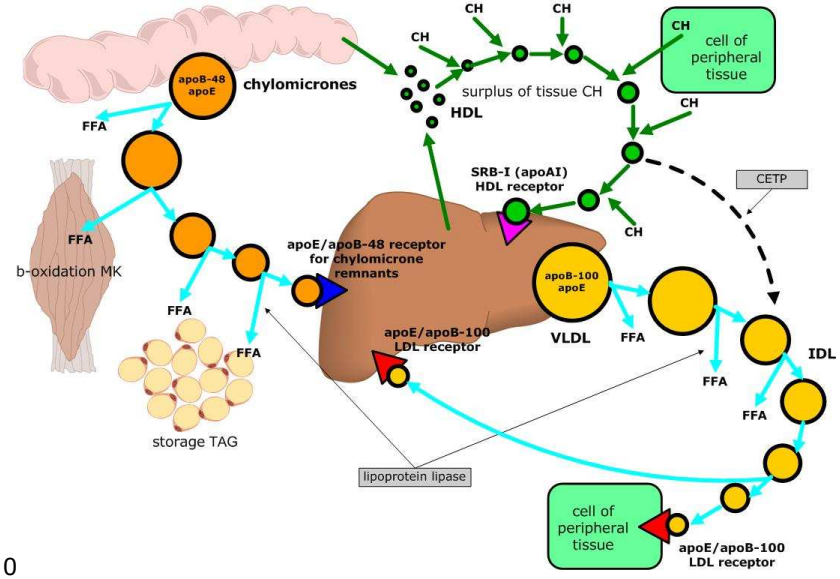
- various types in various lipoproteins – control their metabolic fate
- functions:
  - activation of lipolytic enzymes involved
  - recognition by receptors (→ particle endocytosis)
  - participate in the exchange of lipids between particles
- all particles containing **apoB** (apoB-100 or truncated apoB-48) are **atherogennic**
  - apoB-100 – binding to LDL receptor
  - apoB-48 – binding to the receptor for chylomicron „remnants"
- **apoC** (apoC-II and apoC-III) is a cofactor of LPL (lipoprotein lipase) and thus influence the rate of TAG hydrolysis
- **apoE** influence the removal of lipoprotein "remnants" (chylomicrons and VLDL) by liver
- **apoA** is a part of HDL (binding to HDL receptor) and cofactor of LCAT
  - low levels are atherogennic
- **apo(a)** is homologous with plasminogen → acts as a competitive inhibitor of plazminogen without catalytic activity
  - apo(a) vs. tPA
  - plasmin is an enzyme dissolving fibrin (i.e. blood clots)

| particle | 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** |



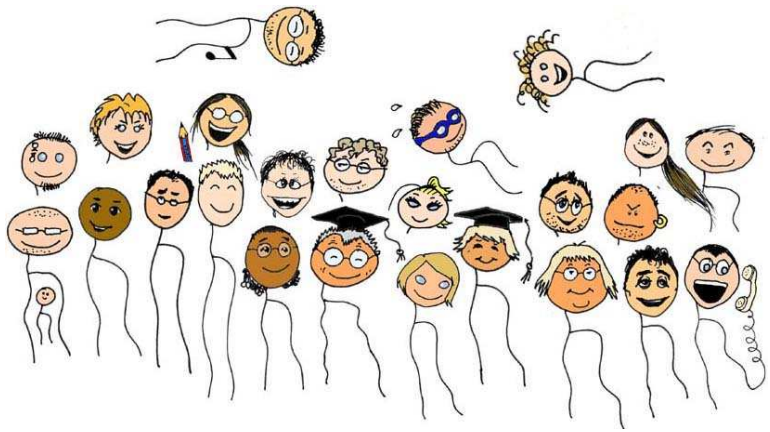



# Overview of lipid transport





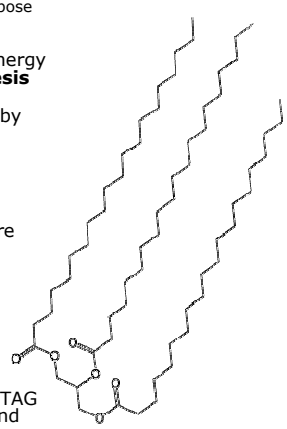

# Triacylglycerides (TAG)



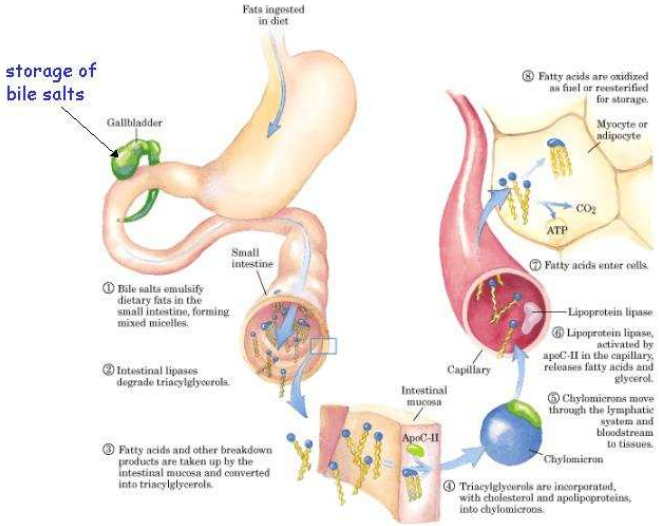


# TAG transport

- **chylomicrons** 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**
  - **insulin** activates LPL and inhibits HSL
  - **catecholamines** and **glucocorticoids** activate HSL
- chylomicrons deprived of dietary TAG form **chylomicron 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

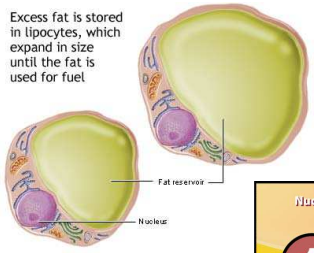


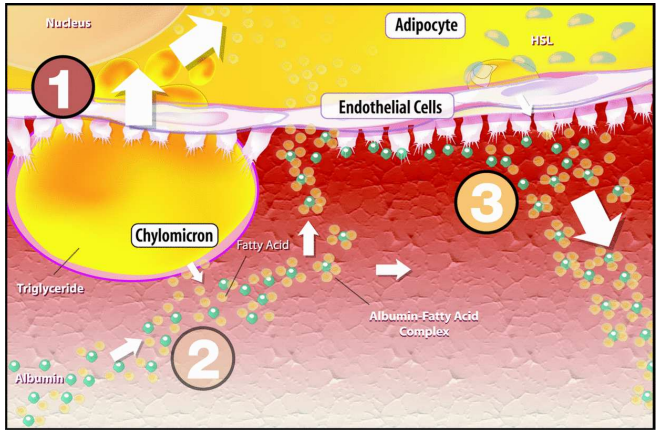
# TAG turnover – summary





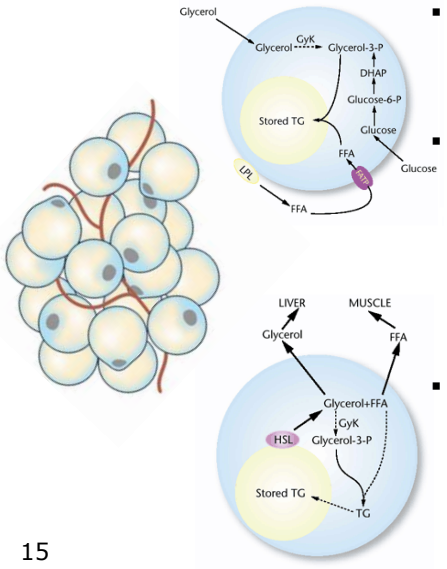

# TAG storage - FA delivery to the adipocyte





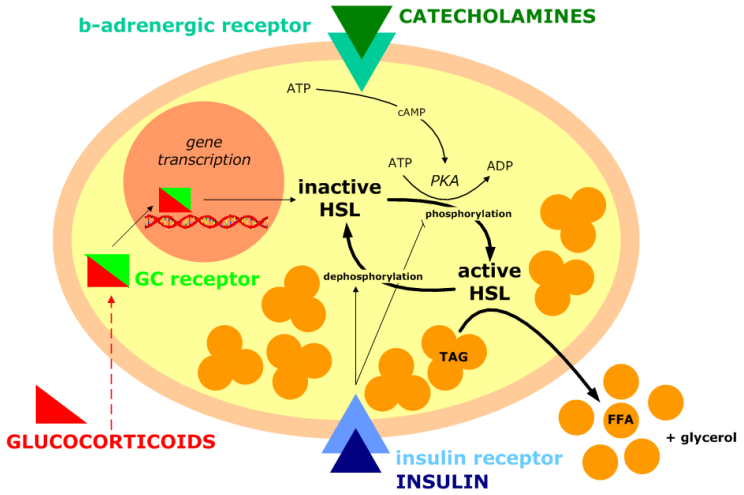

# Regulation of the balance between lipid storage and mobilization in adipocytes




- 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 in liver stimulated by **insulin**
- (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**, …)

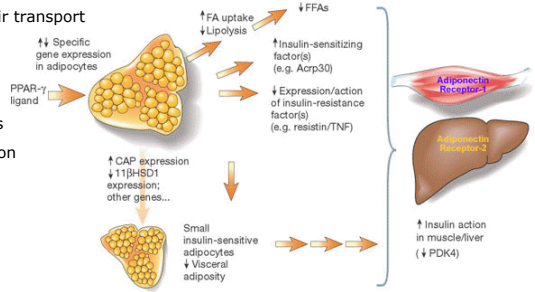


# Hormone-sensitive lipase (HSL)



# Transcriptional regulation of genes involved in TAG metabolism

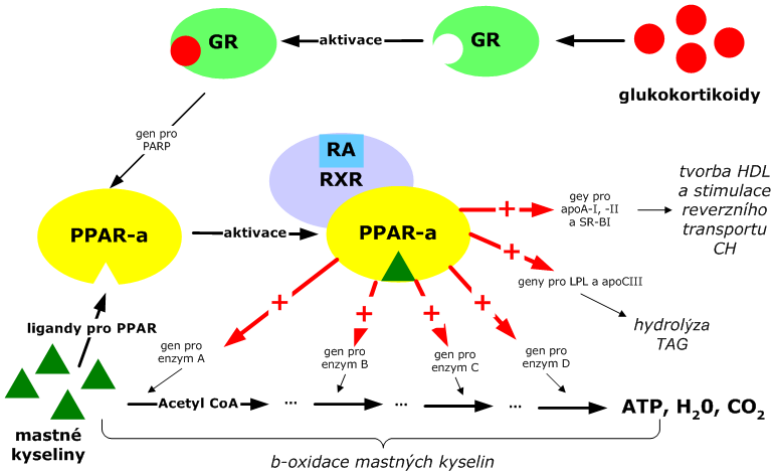
- regulation by transcription factors from the family of nuclear receptors
- **(1) PPARs** (peroxisome proliferator activator receptors)
  - family of nuclear receptors PPARs (PPARα, γ and δ) regulating gene transcription of certain genes under the activation by lipophilic ligands
    - e.g. dietary polyunsaturated fatty acids or prostaglandin derivatives
  - PPAR/RXR heterodimers likely function as a cellular **„lipostat"**
    - PPARα act mainly in liver – activation of FFA 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






# Geny regulované PPARα

- sumární efekt:
  - aktivace oxidace mastných kyselin
  - snížení plazmatických hladin TAG
  - snížení plazmatických hladin CH



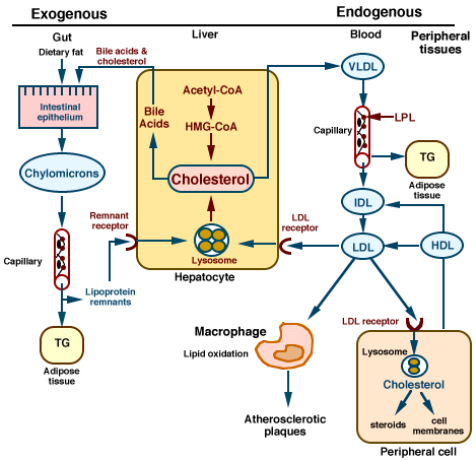



# Cholesterol (CH)



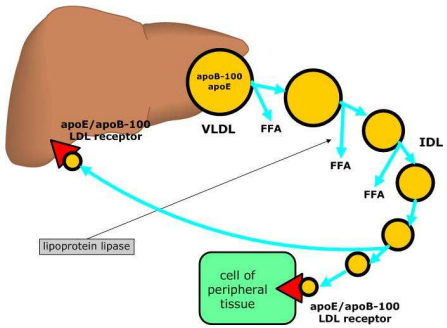

# Overview of CH metabolism

- CH is transported by lipoproteins more or less independently on TAG
- CH is an indispensable for all cells
  - membranes
  - steroid hormones synthesis
  - vitamin D formation
- 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 – see **REGULATION**
- 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



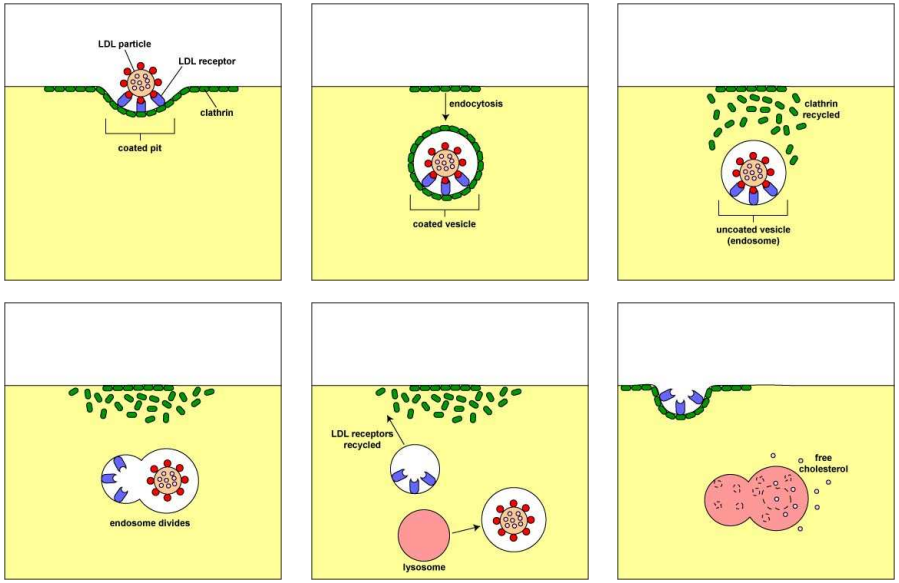
# CH transport – to the periphery

- 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**

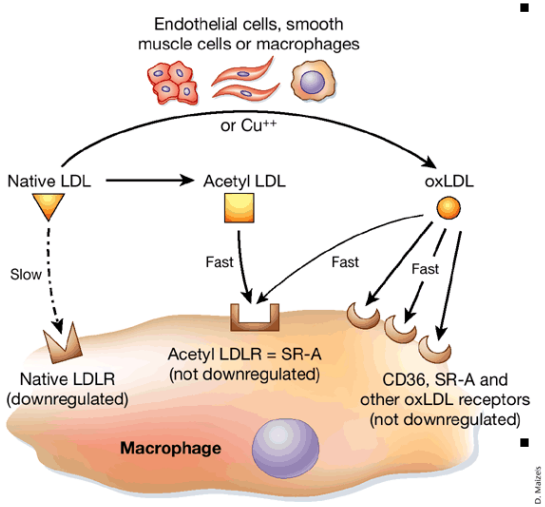





# LDL receptor endocytosis



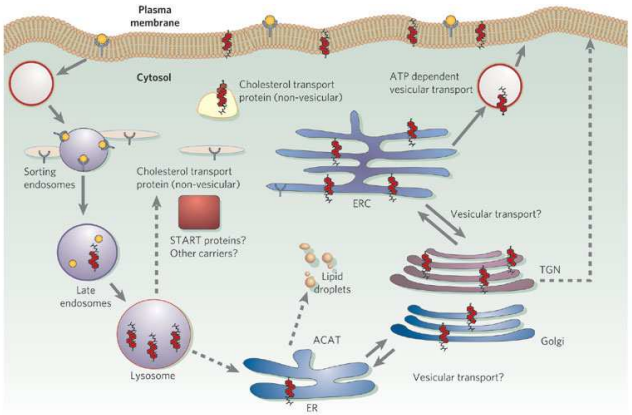

# Non-LDLR-dependent CH uptake




- 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



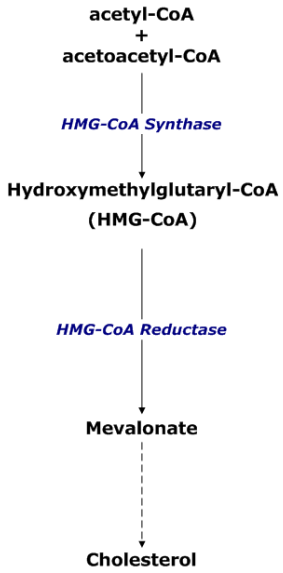
# Overview of intracellular CH




- LDL (yellow circles) carrying CH bound to LDL receptors (light blue Y-shape) is internalized and transported to endosomes and lysosomes from which CH can efflux to cellular compartments including the plasma membrane or the endoplasmic reticulum (ER)
- The LDL receptor recycles to the membrane via the endocytic recycling compartment (ERC)
- Newly synthesized CH in the ER is mostly transported from the ER directly to the plasma membrane, bypassing the Golgi, but some follows the biosynthetic secretory pathway from the ER to the Golgi
- Excess cholesterol in the ER becomes esterified by ACAT and stored in cytoplasmic lipid droplets

# CH homeostatic mechanisms

- optimal cellular content of CH is maintained by several mechanisms:
- (1) excess of free CH is esterified into esters by acylCoA:cholestrol acyltransferase (ACAT) and esters are stored as lipid droplets in cytoplasm from where can be hydrolysed again
- (2) de novo biosynthesis of CH when CH is low
  - 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 (see further)
- (3) efflux of excess CH from the cell by the family of ABC transporters and via reverse CH transport using HDLs





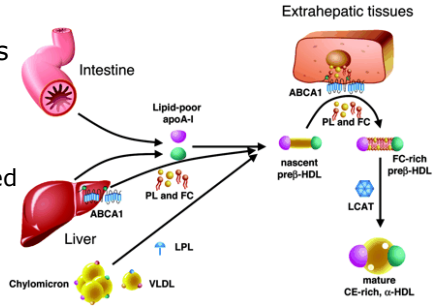

# Regulation of CH synthesis

- **(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)

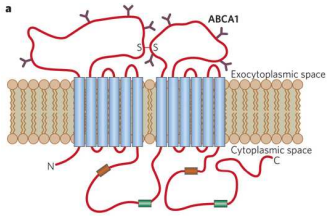
- RCT is mediated by **HDLs formed in liver** and enterocytes
- (1) secretion & lipid acquisition
  - begins with the secretion of lipid-poor apoA-I by liver and intestine followed by acquisition of CH and PL via ABCA1-mediated efflux from the liver
    - **apoA-I** gene expression is regulated by many 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

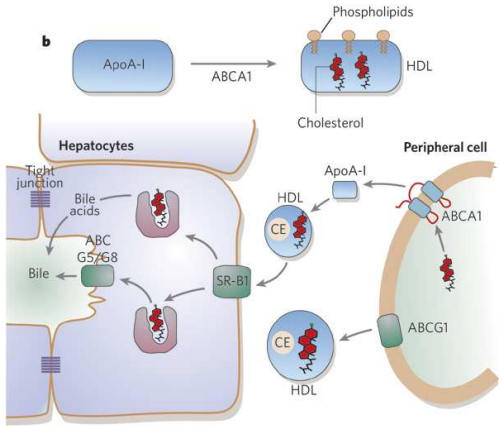





# ATP-binding cassette transporter A1

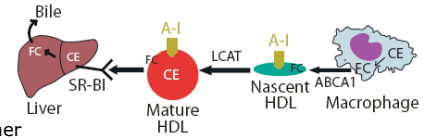
- ABCA1 is a multiple membrane-spanning protein with two nucleotide-binding folds linked by a cytoplasmic peptide sequence
  - mutations in ABCA1 gene lead to **Tangier disease** (↓↓ HDL → atherosclerosis)
- ABCA1 promotes the transfer of CH to lipid-poor forms of ApoA-I HDLs (mechanisms is not fully 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

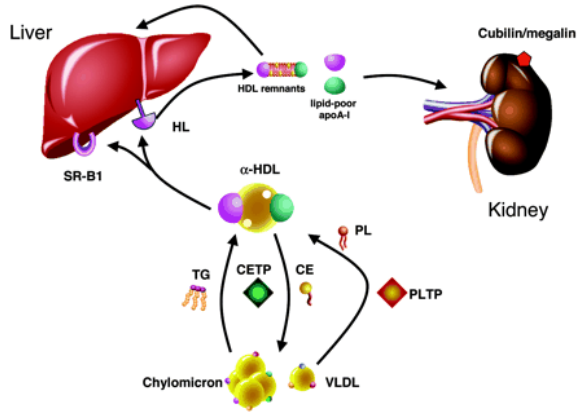



- (3) intravascular modelling of HDL by lipases and lipid transfer factors
  - an important determinant of the rate of HDL clearance from the circulation
  - enzyme **CETP** [cholesterol ester transfer protein]
    - catalyses reverse process - heteroexchange of CHE between HDLs and TAG-rich lipoproteins (chylomicrons and VLDLs) which results in CHE depletion and TAG enrichment of HDL
  - hepatic lipase
    - modification of TAG-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

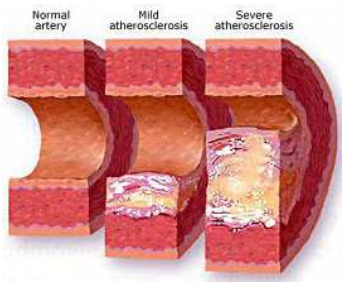
- in summary, efficiency of RCT is determined by:
  - (1) the rate of production of apoAI
  - (2) the rate of clearance of HDLs from circulation by liver (via SR-BI)
  - (3) the rate of CH esterification (↑ LCAT/↓ CETP)
  - (4) action of lipases (hepatic, lipoprotein) – variable TG content influence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



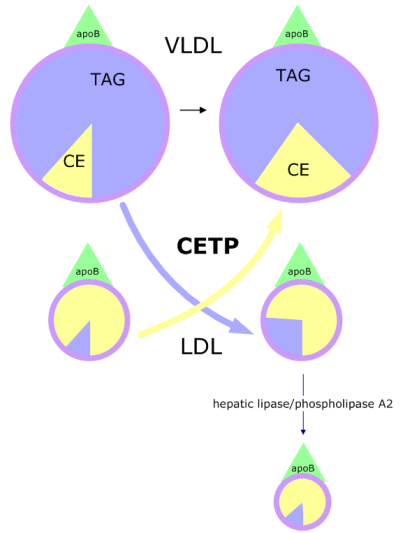

- **hypertriglyceridemia**
  - (1) ↑ isolated TAG (i.e. TAG-rich particles)
    - ☛ solely high TAG is not atherogenic (e.g. LPL deficiency)
  - **– risk of acute pancreatitis ()**
    - ☛ TAG > 20-30 mmol/l
  - (2) ↑ TAG (i.e. TAG-rich particles) + FFA
  - **– insulin resistance**
  - (3) ↑ TAG + ↑ 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

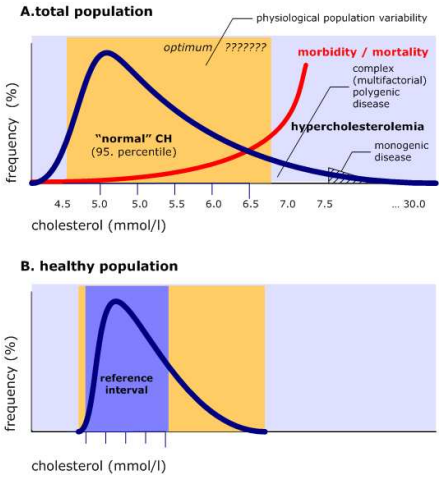
| Type | Particle elevated | Serum CH | Serum TAG | % |
|---|---|---|---|---|
| I | chylom | Normal to ↑ | ↑↑↑↑ | <1 |
| IIa | LDL | ↑↑ | Normal | 10 |
| IIa | LDL and VLDL | ↑↑ | ↑↑ | 40 |
| III | IDL | ↑↑ | ↑↑↑ | <1 |
| IV | VLDL | Normal to ↑ | ↑↑ | 45 |
| V | VLDL and chylom | ↑ or ↑↑ | ↑↑↑↑ | 5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

| 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 diseases
- genetics (disease vs. disposition)
  - polygenic – complex diseases" ("thrifty" genotype)
    - genetic predisposition + environmental factors (diet!!!)
  - monogenic – single gene






# Primary HLPs

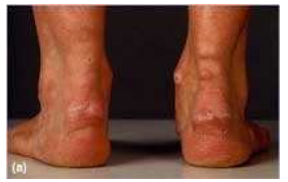
| Disorder | Type (Fredrickson) | Cause |
|---|---|---|
| Familiar deficit of LPL | I | LPL gene mutations |
| Familiar deficit of apoC | I or V | apoC gene mutations |
| Fam. hypercholesterolemia | IIa | LDLR gene mutations |
| Familiar defective apoB-100 | IIa | apoB gene mutations (defect of binding 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) |

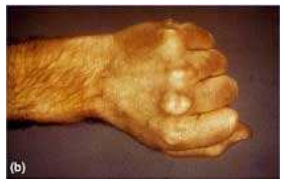
- monogenic diseases are very often **autosomal semidominant**, i.e. severity of the disease is graded according to the number of pathologic alleles
- all primary HLPs typically **do not respond to dietary interventions**, lipid lowering pharmacotherapy is necessary
- carriers are endangered by **premature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

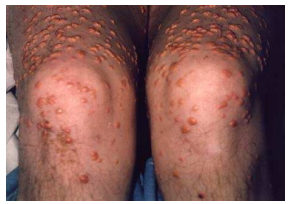


# Familiar hypercholesterolemia (FH)

- 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!!!!



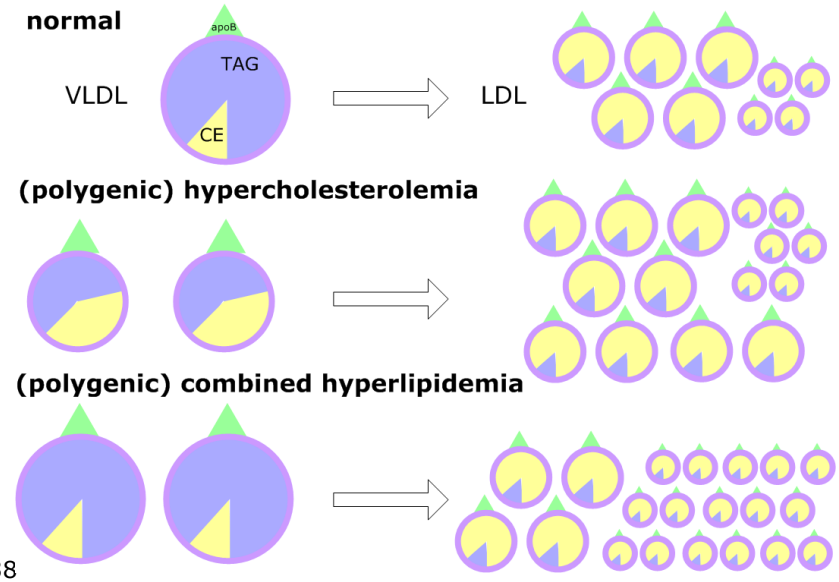



# Polygenic HLPs

- **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)



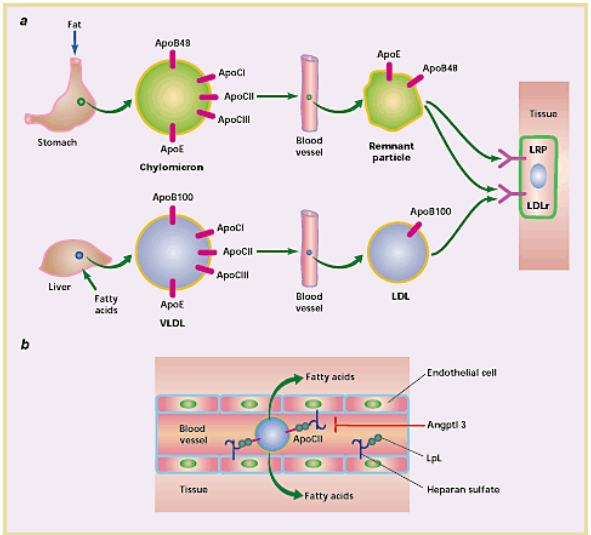
# Lipoprotein profiles – possible findings





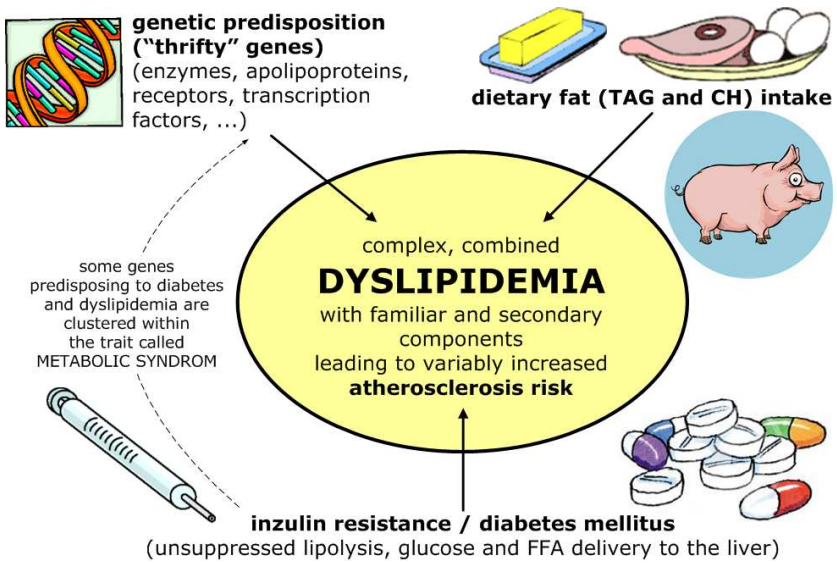

# Common atherogenic dyslipidemias

- 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






# Classification (?) vs. reality(!)



# 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 |