Peroxisome and Lipoprotein Disorders

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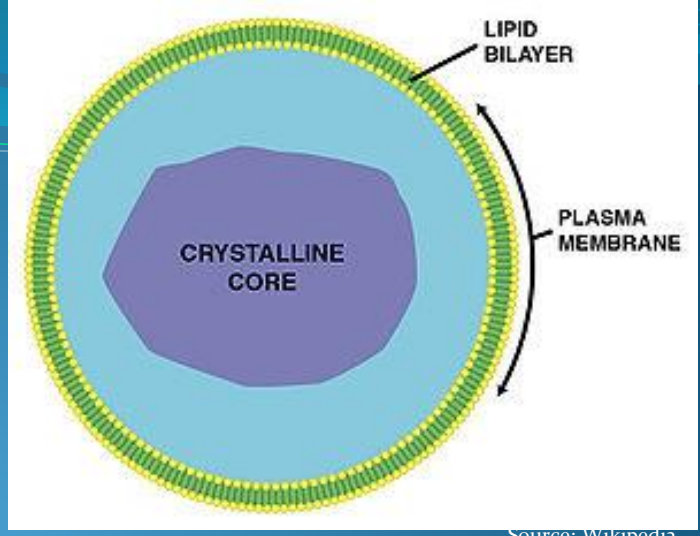
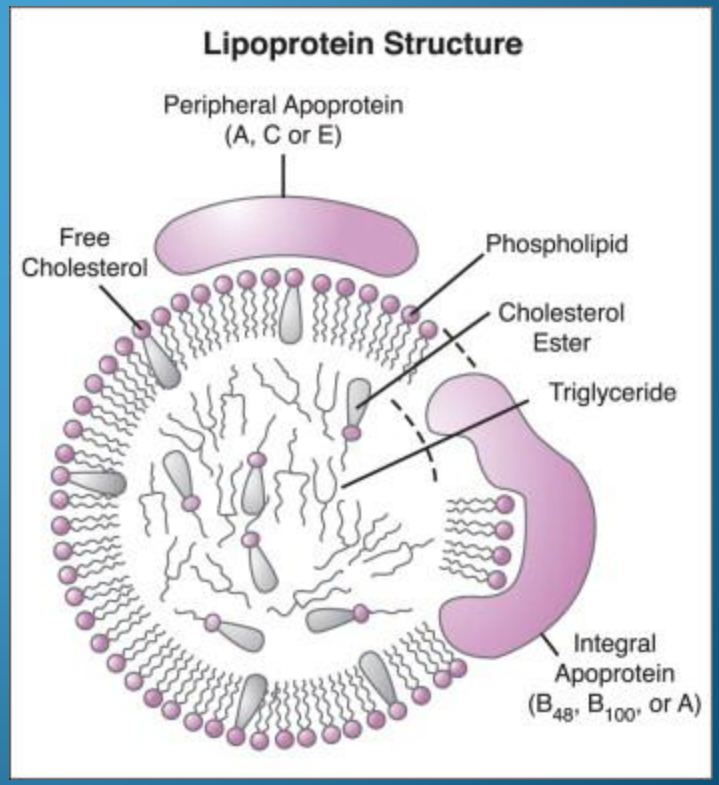


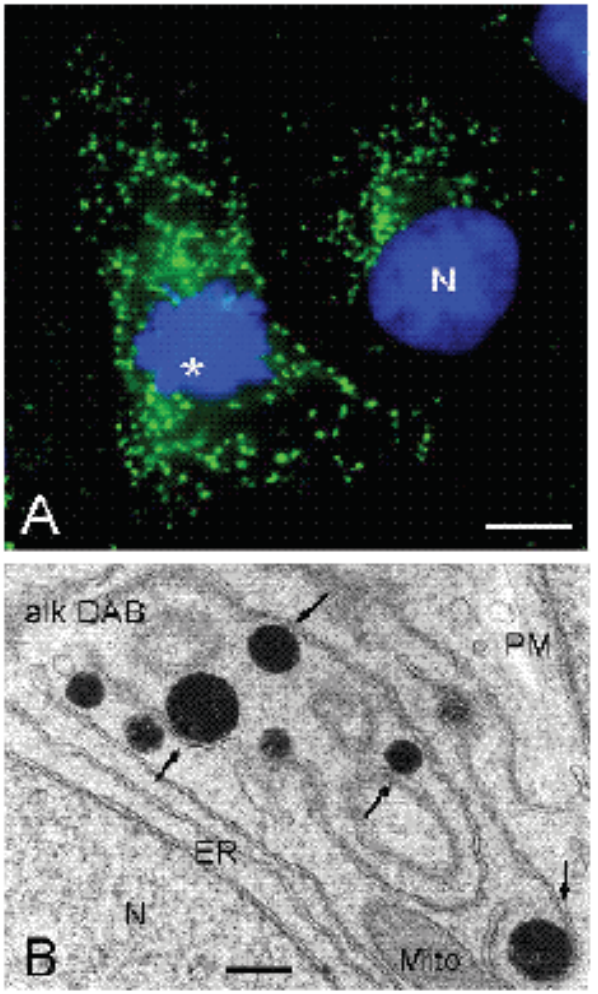
Source: Wikipedia



Source: Larry R. Engelking, in Textbook of Veterinary Physiological Chemistry (Third Edition), 2015

Peroxisomes

- Subcellular compartments virtually present in all eukaryotic cell
- Single membrane bound cell organelle with granular matrix
- Number, size and protein composition depend on cell type
- So called as they perform hydrogen peroxide generating and scavenging activities
- Formed from endoplasmic reticulum and replicate by division
- Have no DNA or ribosomes
- All the proteins first synthesized in the nucleus and transported through specific transport proteins into the organelle
- The transporter proteins present on the surface of organelle and are different for different proteins



A) Green coloured fluorescently tagged Peroxisomes
B) Electron microscopic pic of peroxisomes in rat liver cells

Source: Delille et al 2006. International Journal of Biomedical Sciences; Vol 2 (4)

Peroxisome Functions

- Peroxide metabolism (catalase and H_2O_2-generating oxidases),
- ROS/NOS metabolism
- Lipid biosynthesis (ether phospholipids/plasmalogens, bile acids,
- Cholesterol and dolichol, fatty acid elongation)
- Fatty acid β-oxidation (very long chain fatty acids, dicarboxylic acids, branched chain fatty acids, unsaturated fatty acids, arachidonic acid metabolism, and xenobiotic compounds)
- Fatty acid α-oxidation (phytanic acid, xenobiotic compounds)
- Catabolism of amino acids
- Catabolism of polyamines
- Catabolism of purines
- Glyoxylate detoxification
- Hexose monophosphate pathway

Inherited Peroxisome Disorders

- Congenital diseases
- Caused due to defect in the peroxisomal gene
- More than 25 disorders known till date
- Disorders are subdivided into two major categories:
  - **Peroxisome Biogenesis Disorders-** Failure to form intact or normal peroxisomes. Leads to multiple metabolic abnormalities
  - **Peroxisomal single protein defect- Deficiency of single peroxisomal enzyme**

Inherited Peroxisome Disorders

- **Peroxisome Biogenesis Disorders-**
  - Zellweger syndrome
  - Neonatal adrenoleukodystrophy (NALD)
  - Infantile Refsum's disease (IRD)
  - Rhizomelic chondrodysplasia punctata type 1 (RCDP)

Peroxisomal single protein defect

- X-linked adrenoleukodystrophy (X-ALD)
- Contiguous ABCD1/DX1357E deletion syndrome
- Pseudo-neonatal ALD (acyl-CoA oxidase deficiency)
- D-bifunctional protein deficiency/multifunctional protein 2 deficiency
- Acatalasaemia
- Refsum's disease (phytanol-CoA hydroxylase deficiency)
- Rhizomelic chondrodysplasia punctata type 2
- Rhizomelic chondrodysplasia punctata type 3
- Hyperoxaluria type 1 (Alanine glyoxylate aminotransferase deficiency)
- Mulibreynanism
- a-Methylacyl-CoA racemase deficiency
- Glutaryl-CoA oxidase deficiency (glutaric aciduria type 3)

Signs and Common Symptoms of Peroxisome Biogenesis Disorders-

- **Ghost** peroxisomes are created
- Multiple biochemical abnormalities
- **Organs affected in most peroxisomal disorders include brain, spinal cord, or peripheral nerves, eye, ear, liver, kidney, adrenal cortex, Leydig cells in testis, skeletal system, and in some instances cardiovascular system, thymus, and pancreas**
- Symptoms appear usually at early age of childhood
- In Zellweger syndrome neurodegeneration occurs and early death
- Whereas NALD, IRD and RCDP are mild and have better life span

Signs and Common Symptoms of most common Peroxisomal single protein defects

- X-linked adrenoleucodystrophy
  - caused by a missing or defective protein called ALDP which is crucial for the transport of VLCFA from the cell into the peroxisome .
  - Leading to the accumulation of very long chain fatty acids (VLCFA)(C24 & C26 chain length).
  - VLCFA are attached to gangliosides and cerebrosides accumulate in the white matter of the brain and peripheral nerves and the adrenal cortex.
  - Hence patients develop loss of myelin and adrenal dysfunction due to damage to the adrenal cortex.

- Other hereditary deficiencies are based on mutations in individual β-oxidation enzymes or enzymes involved in ether phospholipid biosynthesis.

- Most of the disorders are lethal

- They are characterized by an accumulation of glyoxylate and oxalate in tissues and body fluids, specifically urine, leading to the precipitation of calcium oxalate and renal failure.

Diagnosis and therapeutic approaches

DIAGNOSIS

- Laboratory diagnosis involves blood and urine analysis viz.

  - plasma VLCFA analysis
  - analysis of plasmalogens in erythrocytes
  - alphaoxidation of phytanic acid
  - biochemical and morphological studies of patient's fibroblasts

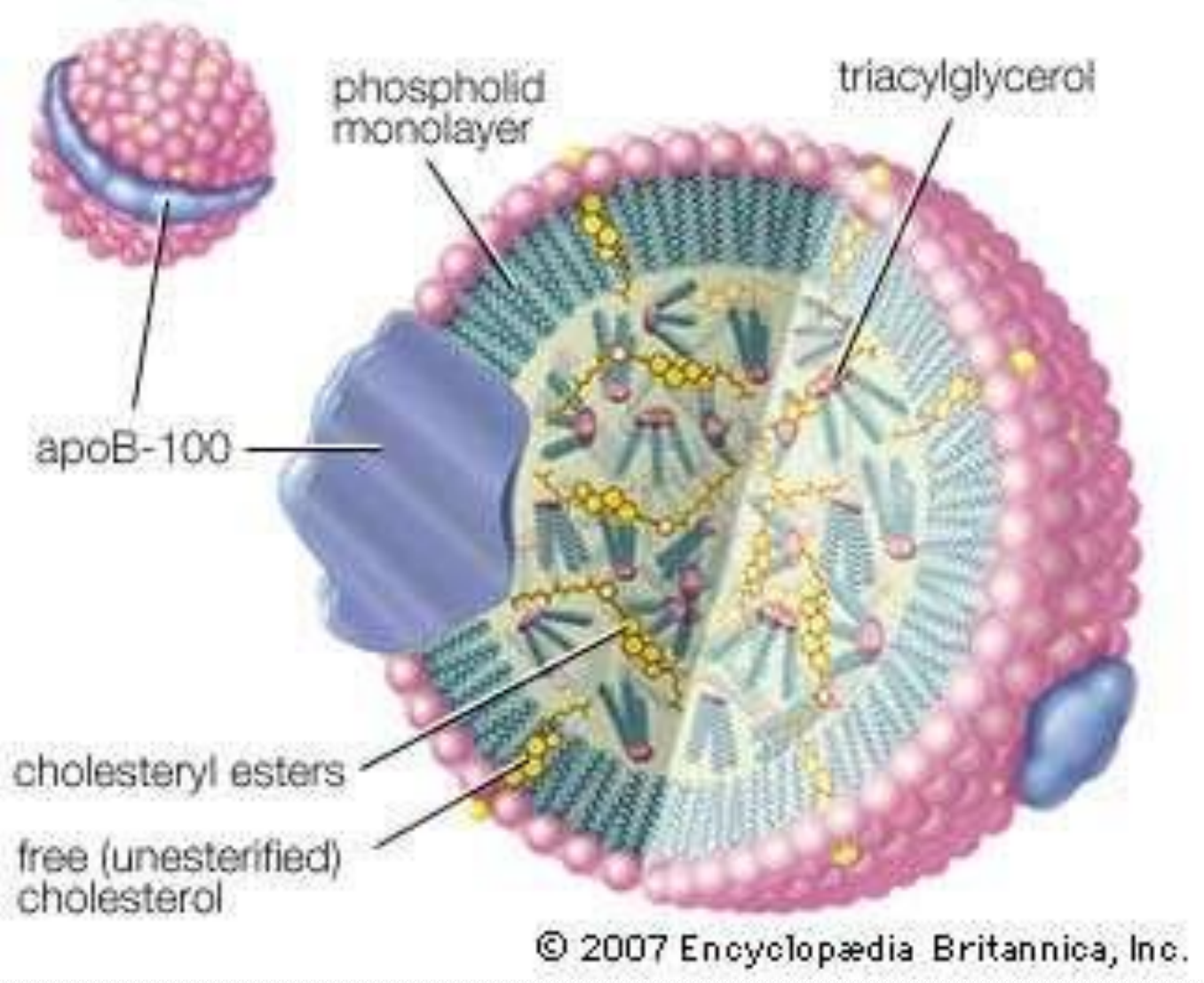
THERAPIES

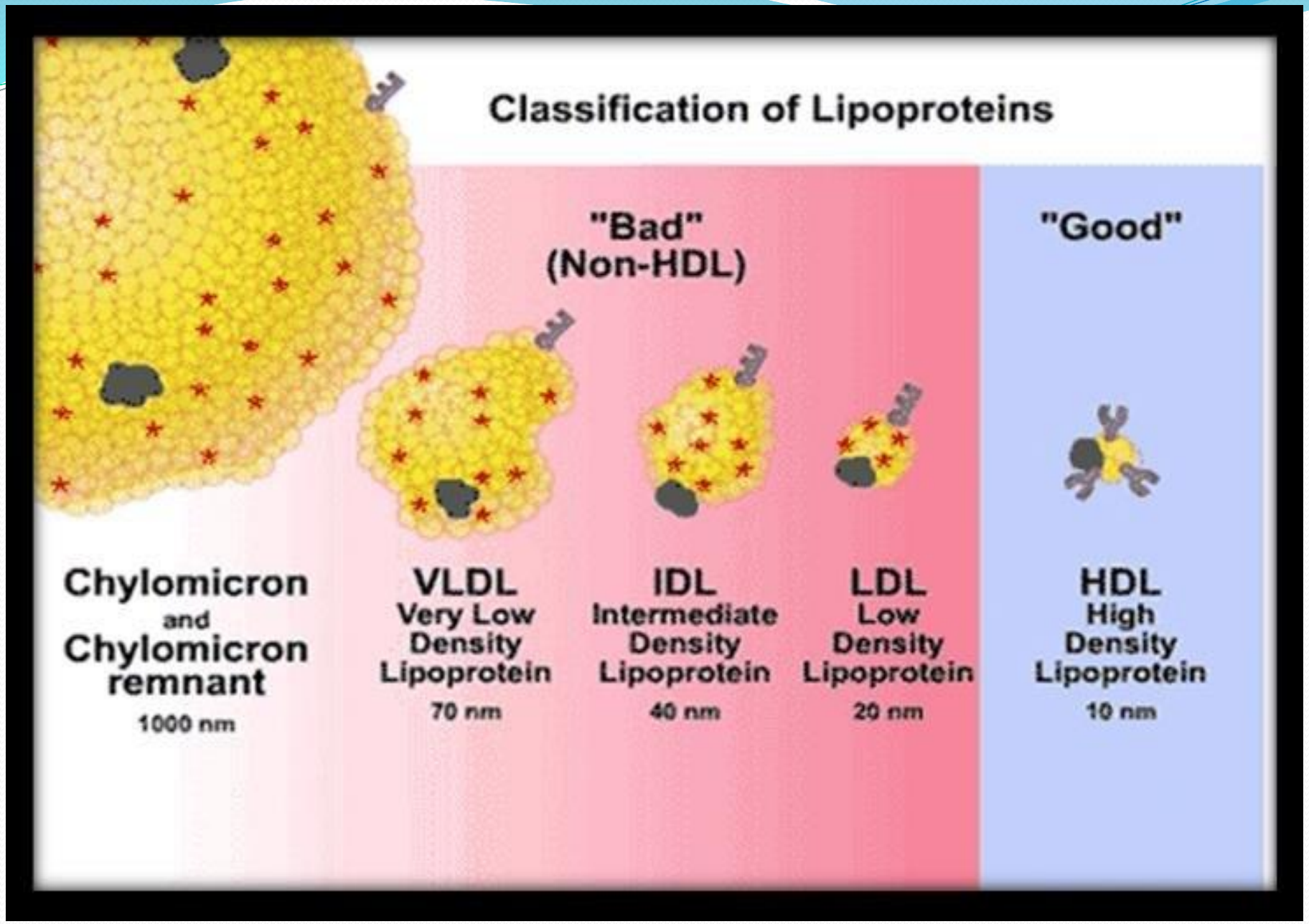
- Reduction of accumulated precursors
- Replacement of Deficient products

Lipoprotein

- Lipoprotein consists of a nonpolar core and a single surface layer of amphipathic lipids
- The nonpolar core consists of mainly triacylglycerol and cholesteryl ester and is surrounded by a singlye surface layer of phospholipids.
- The protein moiety of the lipoprotein is known as **Apoprotein** or **Apolipoprotein**

Structure of Lipoprotein



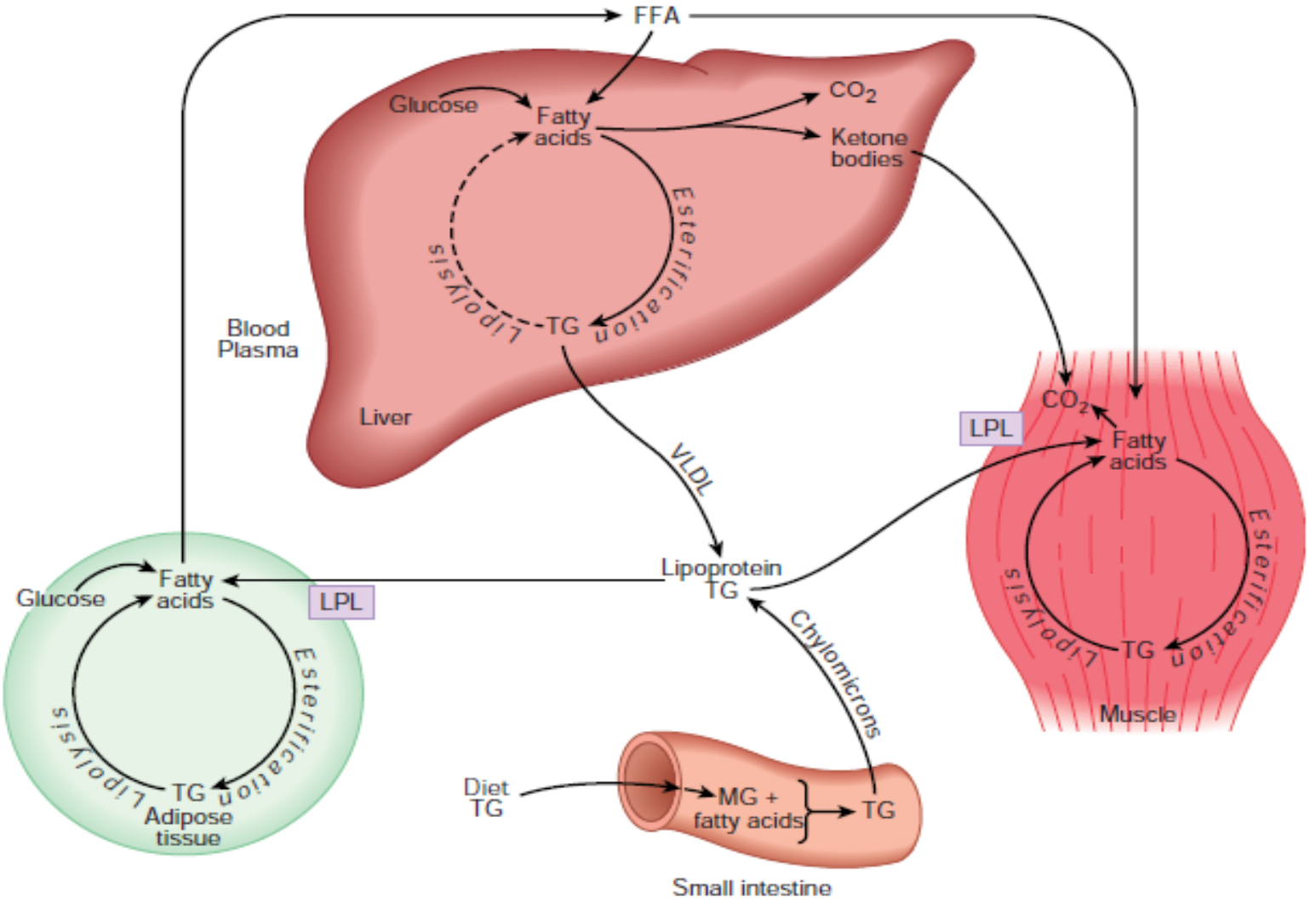


Source: Thesis of Isam Karam

Apolipoproteins

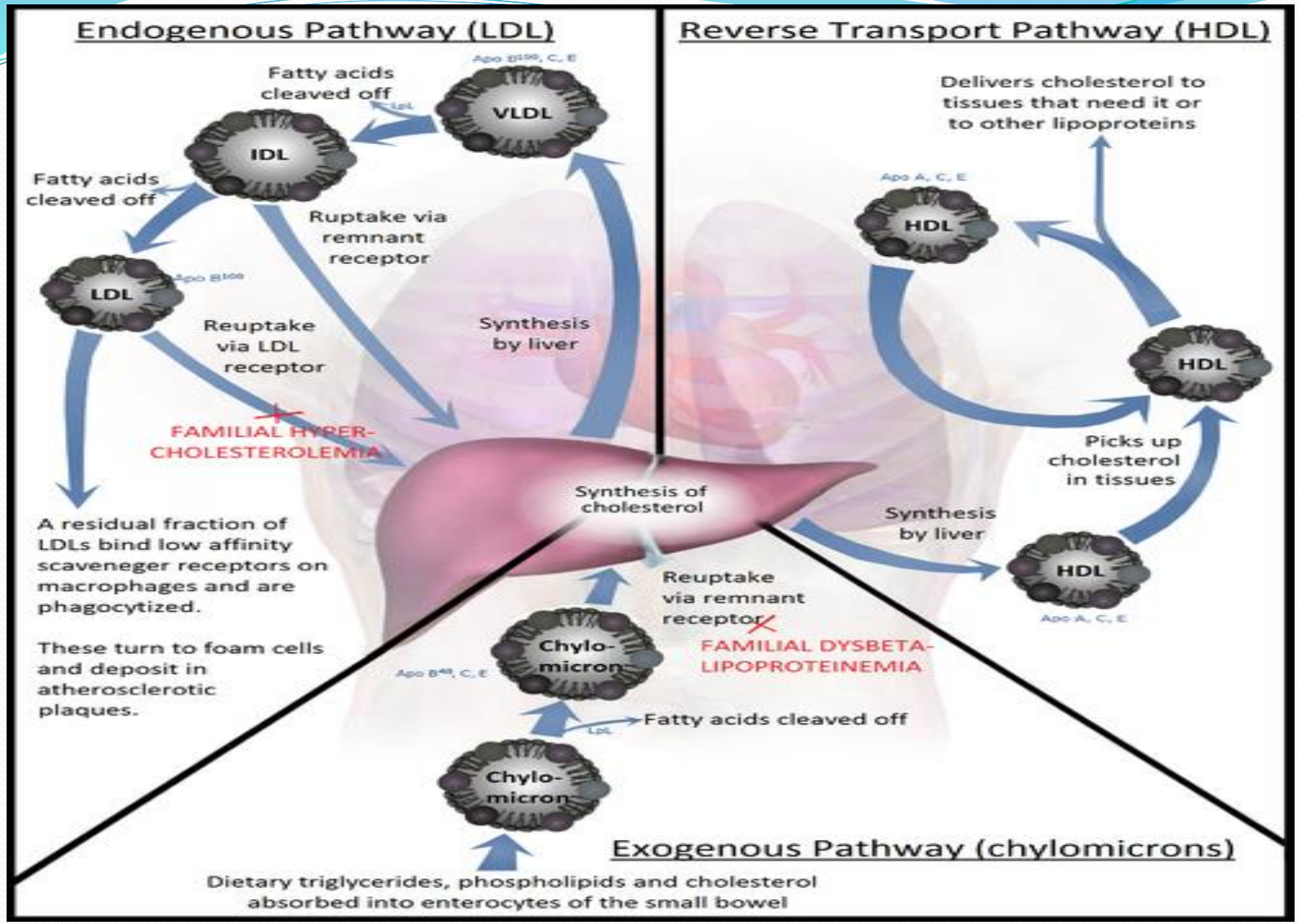
- **One or more apolipoproteins are present in each lipoprotein**
- **Apolioproteins of HDL (α- lipoprotein) is designated as "A"**
- **Apolioproteins of LDL (β- lipoprotein) is designated as "B" (B-100)**
- **Chylomicons contain a truncated form of Apo B (B-48)**
- **Apo E is found in VLDL, HDL, Chylomicons and Chylomicons reminants**

Transport and fate of major lipid substrates and metabolites



FFA, free fatty acids; LPL, lipoprotein lipase; MG, monoacylglycerol; TG, triacylglycerol; VLDL, very low density lipoprotein. Source: Harper's Biochemistry 28th edition

Metabolism of Lipoprotein



Source: https://en.wikipedia.org/wiki/Lipoprotein

Disorders of Lipoproteins

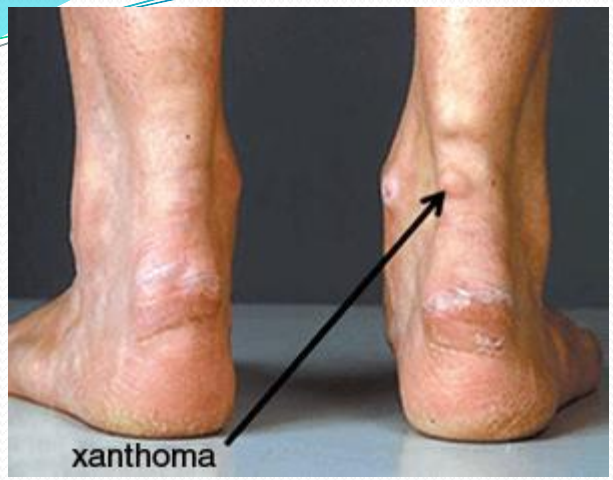
S. No.	Disorder	Defect	Characteristics
1.	**Hypolipoproteinemias** Abetalipoproteinemia	No chylomicrons, VLDL, or LDL are formed because of defect in the loading of apo B with lipid.	Rare; blood acylglycerols low; intestine and liver accumulate acylglycerols. Intestinal malabsorption. Early death avoidable by administration of large doses of fat-soluble vitamins, particularly vitamin E.
2	Familial alpha-lipoprotein deficiency Tangier disease Fish-eye disease Apo-A-I deficiencies	All have low or near absence of HDL.	Tendency toward hypertriacylglycerolemia as a result of absence of apo C-II, causing inactive LPL. Low LDL levels. Atherosclerosis in the elderly
3	Hyperlipoproteinemias Familial lipoprotein lipase deficiency (type I)	Hypertriacylglycerolemia due to deficiency of LPL, abnormal LPL, or apo C-II deficiency causing inactive LPL	Slow clearance of chylomicrons and VLDL. Low levels of LDL and HDL. No increased risk of coronary disease.
4	Familial hypercholesterolemia (type IIa)	Defective LDL receptors or mutation in ligand region of apo B-100	Elevated LDL levels and hypercholesterolemia, resulting in atherosclerosis and coronary disease.

Contd...

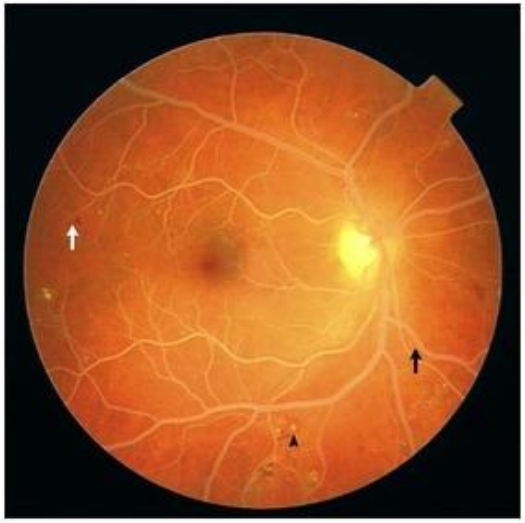
5	**Familial type III hyperlipoproteinemia (broad beta disease, remnant removal disease, familial dysbetalipoproteinemia**	**Deficiency in remnant clearance by the liver is due to abnormality in apo E. Patients lack isoforms E3 and E4 and have only E2, which does not react with the E receptor**	**Increase in chylomicron and VLDL remnants of density < 1.019 (β-VLDL). Causes hypercholesterolemia, xanthomas, and atherosclerosis**
6	Familial hypertriacylglycerolemia (type IV)	Overproduction of VLDL often associated with glucose intolerance and hyperinsulinemia	Cholesterol levels rise with the VLDL concentration. LDL and HDL tend to be subnormal. This type of pattern is commonly associated with coronary heart disease, type II diabetes mellitus, obesity, alcoholism, and administration of progestational hormones.
7	Familial hyperalphalipoproteinemia	Increased concentrations of HDL.	A rare condition apparently beneficial to health and longevity
8	Hepatic lipase deficiency	Deficiency of the enzyme leads to accumulation of large triacylglycerolrich HDL and VLDL remnants	Patients have xanthomas and coronary heart disease
9	Familial lecithin:cholesterol acyltransferase (LCAT) deficiency	Absence of LCAT leads to block in reverse cholesterol transport. HDL remains as nascent disks incapable of taking up and esterifying cholesterol.	Plasma concentrations of cholesteryl esters and lysolecithin are low. Present is an abnormal LDL fraction, lipoprotein X, found also in patients with cholestasis. VLDL is abnormal (β-VLDL).
10	Familial lipoprotein(a) excess	Lp(a) consists of 1 mol of LDL attached to 1 mol of apo(a). Apo(a) shows structural homologies to plasminogen	Premature coronary heart disease due to atherosclerosis, plus thrombosis due to inhibition of fibrinolysis

Source: Harpers' Biochemistry 28th Edition

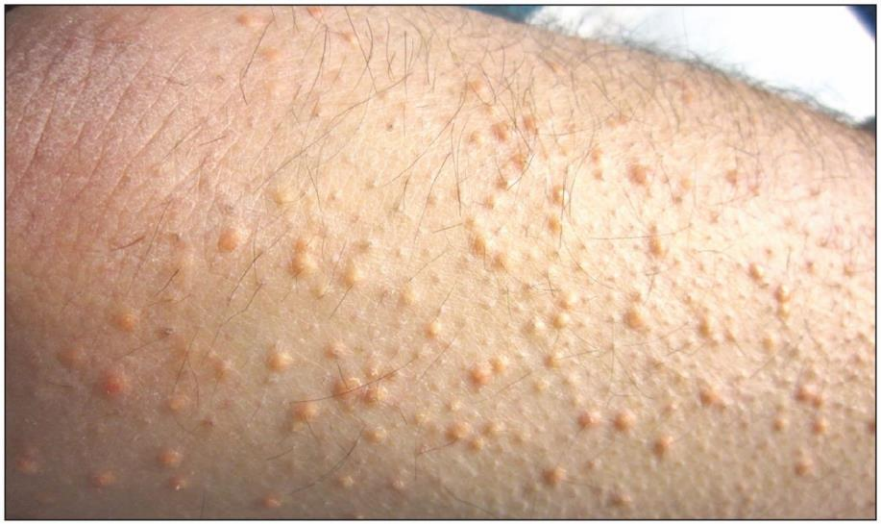
Clinical Features & Drugs



Xanthoma of elevated LDL patient



Eruptive Xanthoma of elevated LDL patient



Eruptive Xanthoma of elevated LDL patient

- Thank you