FUND

WEEK 4

LIPID, CHOLESTEROL
NUTRITION cell biology

THIS WEEK:

- Q → Clinical Informatics
- Cholesterol/Mevalonate Pathway
- Familial Hypercholesterolemia
- Q → Genome Wide Association Studies
- Nutrition
- Q → Intercellular Junctions
- Q → Protein Sorting / Secretory Pathway
- Q → Embryology - Body Cavities
- Q → Anatomy - Limbs
- Q → Histology - Blood Cells, Connective Tissue
- Lipoproteins
- Coronary Artery Disease
- LDL Workshop

like triglycerides, cholesterol can be sourced EXOGENOUSLY or made ENDOGENOUSLY — diff. pathways for both → mechanism for transport in circulation needed

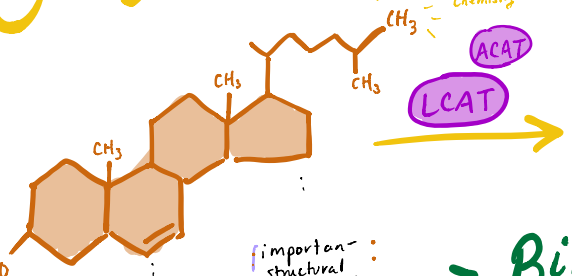
ENDOGENOUS

IN LIVER: all tissues can make cholesterol but liver main regulator!

2-acetyl-CoA
↓ thiolase
thiolase
↓ HMG CoA synthase
HMG CoA
↓ HMG CoA lyase
Acetoacetate ⇄ β hydroxy butyrate
Acetone
KB
HMG CoA reductase
R.L.S.!!!
STATINS
mevalonate
↓
cholesterol

bloodstream

cholesterol



HD site of esterification

turns into these important things
- hormones: estrogen, progesterone, testosterone, cortisol, aldosterone
- vitamins: vitamin D
- bile acid

important structural component for cell/organelle membranes

Bile Acid

(+ glycine / + taurine = more soluble bile salt)

facilitates absorption of dietary cholesterol through micelle formation, lipase activity

exogenous

route for cholesterol excretion

BILE SALTS

75%

travels in bloodstream

25%

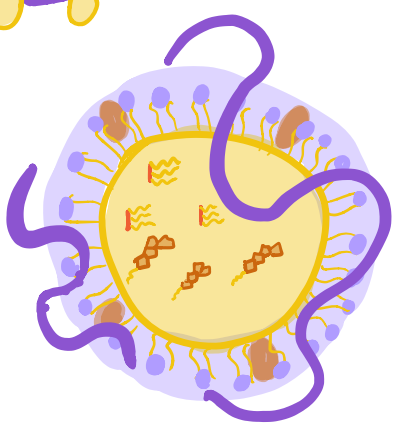
EXOGENOUS

from our diet

absorbed in intestine (GI)

LIPOPROTEINS

efficiently shuttles cholesterol + fat through plasma



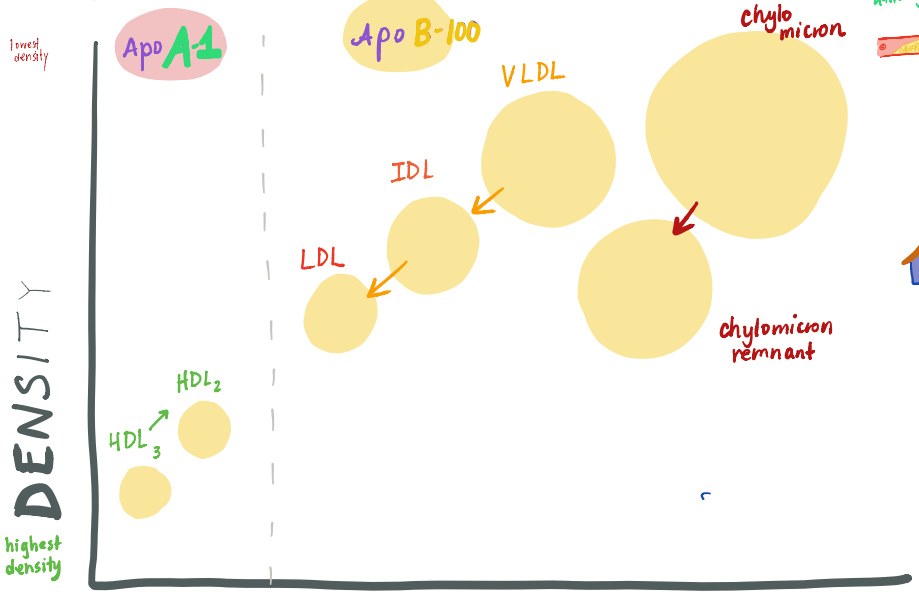
Core: triglycerides, cholesterol ester } hydrophobic
→ more efficient to be in core (SA to V)

Coat: phospholipids, unesterified cholesterol, apolipoproteins
→ shuttle that interacts w/ various enzymes & receptors to facilitate cholesterol transport & metabolism

acts as ligand for liver receptors

CLASSES OF APOLIPOPROTEINS

- B-48 — intestinal secretion of chylomicrons exog.
- anti-atherogenic A-1 — activates LCAT
- B-100 — transport of endogenous cholesterol
- C-II ↑ LPL — lipoprotein lipase cofactor/activator
- C-III ↓ LPL — decr LPL activity
- E — mediates remnant uptake into liver



DIAMETER →

based on density & size
more protein = MORE DENSE

Main classes of lipoproteins

another way to look @ composition

Lipoprotein	Density	%PL	%Ch	%CE	%TGs	%protein	Main Apo
Chylomicrons	lowest	10	5	15	65	5	B-48 (A-I, A-II, C-II, C-III, E)
VLDL	very low	15	5	15	55	10	B-100 (C-II, C-III, E)
IDL	interme diate	20	10	28	22	20	B-100, E
LDL	low	22	10	36	12	20	B-100
HDL	high	24	2	20	4	50	A-I, A-II (C-II, C-III, E)

Important Receptors

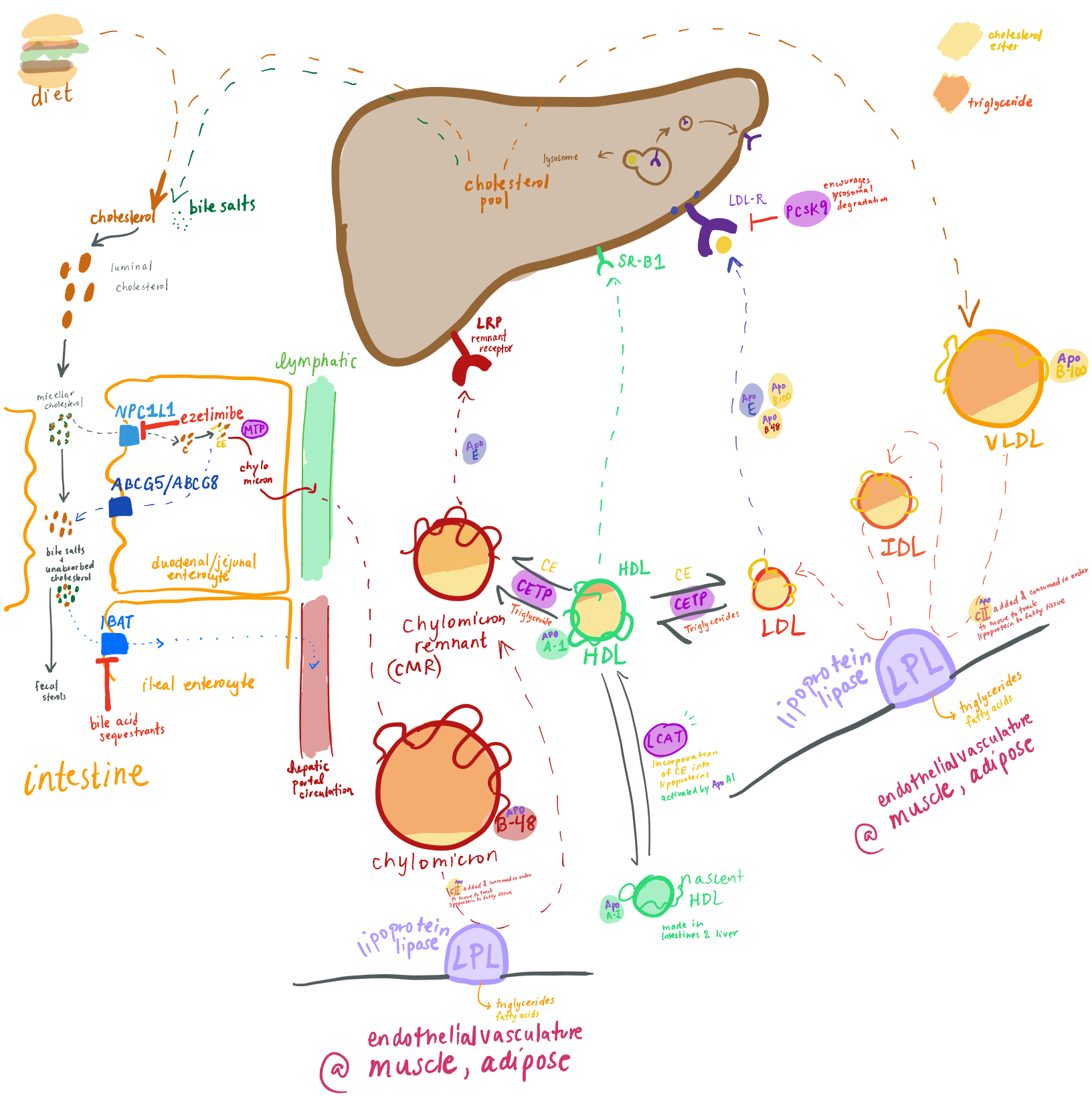
Protein	Location	Function
LDLr	Basolateral hepatocyte surface, also many other tissues	Binding and internalization of ApoB-containing lipoproteins, mostly LDLs and IDLs,
SR-B1	Basolateral hepatocyte surface, steroidogenic organs	Accepts cholesterol from HDLs
LRP1, remnant receptor	Basolateral hepatocyte surface, also many other tissues	Binding and internalization of chylomicron remnants, VLDL remnants, IDLs

Important Enzymes

Enzyme	Location	Function
CETP (cholesteryl ester transfer protein)	plasma	Shuttles CE for TG between lipoproteins
PLTP (phospholipid transfer protein)	plasma	Shuttles PL between lipoproteins
LPL (lipoprotein lipase)	vascular endothelium	TG lipolysis (chylomicrons, VLDL, IDL)
HL (hepatic lipase)	hepatic endothelium	TG and phospholipid lipolysis (IDL, LDL, HDL), lipoprotein uptake
LCAT (lecithin cholesterol acyltransferase)	HDL	Esterification of cholesterol

Other important PROTEINS

Protein	Location	Function
NPC1L1	Luminal surface of enterocytes	Transfers sterols into enterocyte
ABCG5/8	Luminal surface of enterocytes, Biliary surface of hepatocytes	Expels sterols back to gut lumen, expels sterols to bile
MTP	ER and Golgi of enterocytes, hepatocytes	Synthesis of chylomicrons and VLDLs
ABCA1, ABCG2	Plasma membrane of macrophages and other cells	Cholesterol efflux to nascent and growing HDL particles



HOW DO WE TEST FOR AUTOANTIBODIES?

- LPL
- LDL receptor

use plasma of patient as reagent!

ELISA, western blot

Enzymatic protein defect – Assay recessive → "appears to be sporadic"

Structural protein defect – DOMINANT inheritance

Dyslipidemias

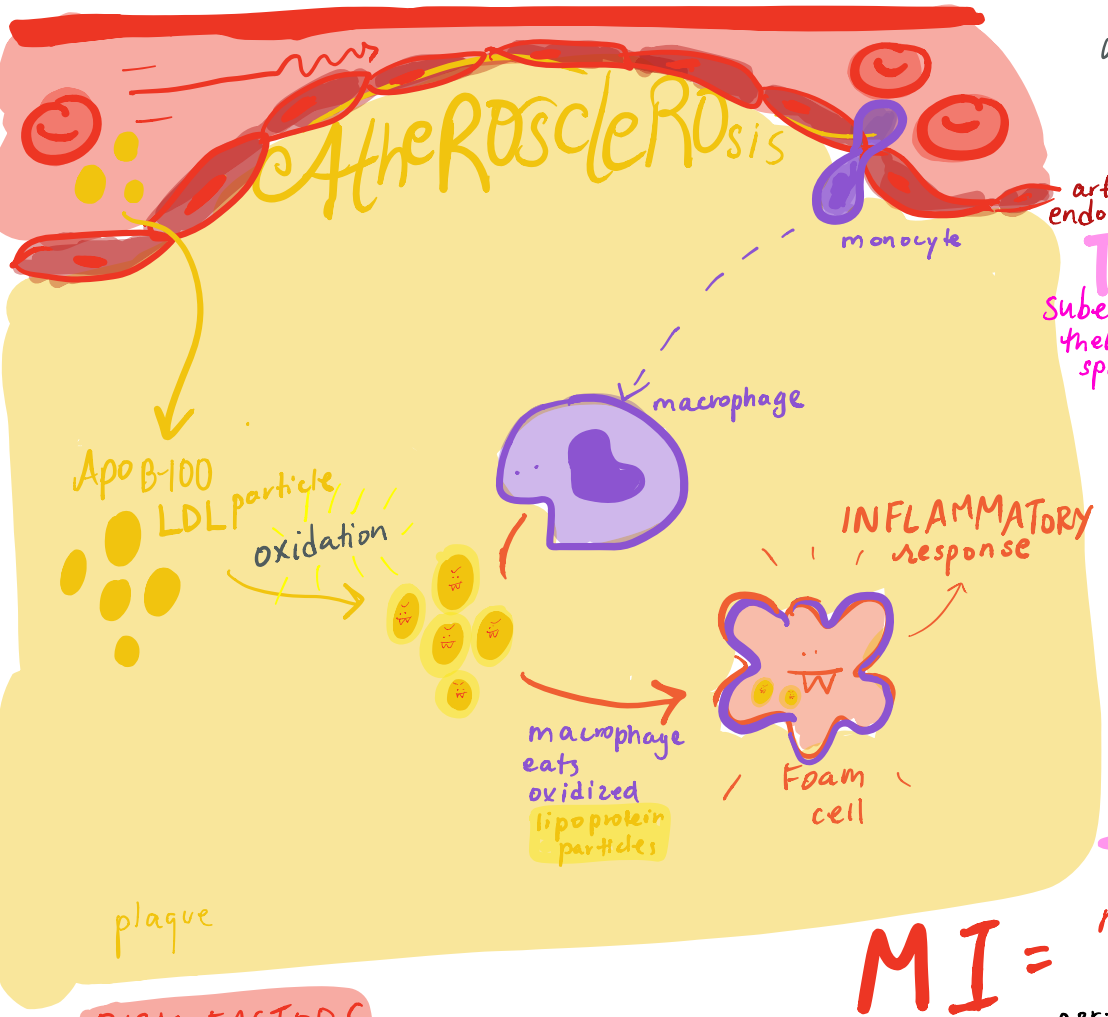
		defect in...	Sx
I	Hypercholesterolemia (AR)	∅ LPL, Apo C-II	impaired vision is not a symptom ↑ chylomicron, TGs, cholesterol no incr. risk for atherosclerosis pancreatitis "WHITE" BLOOD 1% milk → type IIb
II	Familial Hypercholesterolemia (AD) ↳ South Africans ↳ French Canadians	∅ LDL-R (apoB, PCSK9, LDLR AP1) ↓ less frequent	180 / 150 ↑ LDL, cholesterol, VLDL accelerated atherosclerosis corneal arcus extensor tendon xanthomas early onset aortic valve stenosis
III	Dysbetalipoproteinemia (AR)	∅ ApoE	↑ chylomicron, VLDL premature atherosclerosis palmar & tuberoeruptive xanthomas
IV	Hypertriglyceridemia (AD)	hepatic overproduction of VLDL	↑ VLDL, TG pancreatitis
	Cerebrotendinous Xanthomatosis	defect in CYP27A1	↓ bile acid synthesis ↑ cholestanol tx: chenodeoxycholic acid tendon xanthomas, brain Xa cataracts atherosclerosis
	sitosterolemia	defect in ABCG5 or ABCG8	↑ hyperabsorption of plant sterol + cholesterol ↓ excretion of sterols in bile early onset tendon xanthomas, hemolytic anemia
	niemann-pick dz	defect in NPC1L1	

DRUGS to treat hypercholesterolemia

most effective @ lowering LDL-C, the cholesterol within LDL particle

- statins ..... ↑ presence of PCSK9 → incr ↑ LDL-R lysosomal degradation!
- α-PCSK9 antibodies $$$
- bile acid sequestrants
- fibrates (gemfibrozil, fenofibrate)
- ezetimibe
- dietary intervention

atherosclerosis



lipo
atherogenic proteins have Apo B-100, 90% LDL, but also VLDL IDL CMR

recall that lots of small LDLs WORSE than fewer large LDLs

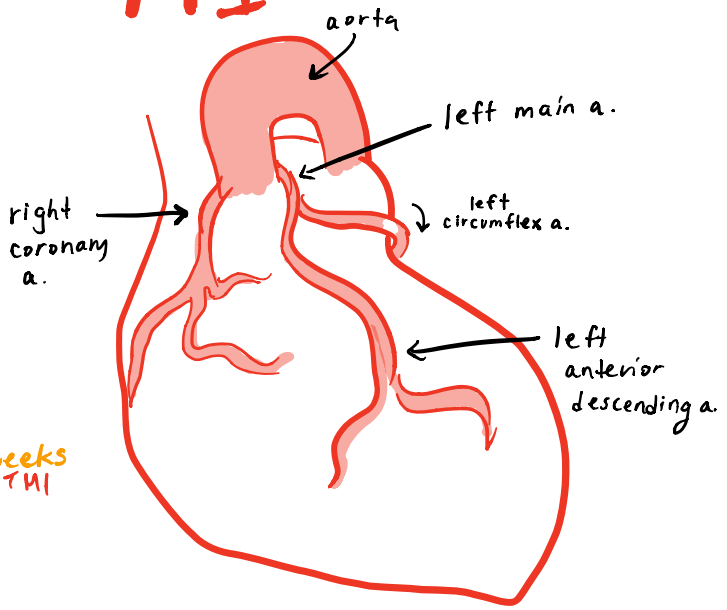
incr. risk of atherosclerosis

RISK FACTORS

"non modifiable"
- age
- family hx
- ethnicity
- biological sex

"modifiable"
- smoking
- elevated cholesterol
- sedentary lifestyle
- stress
- obesity
- insulin resistance
- diabetes
- alc. in excess

MI = myocardial infarction



! SX

1.
2.
3.
4.

! 12-24 hrs POST MI → 24-48 hrs POST MI → 2 weeks POST MI

→ PUT THESE HISTOLOGY FINDINGS in chronological order, and under the right time category.
- fibroblast proliferation
- necrosis
- lymphocytic infiltrate
- eosinophilia
- connective tissue scar