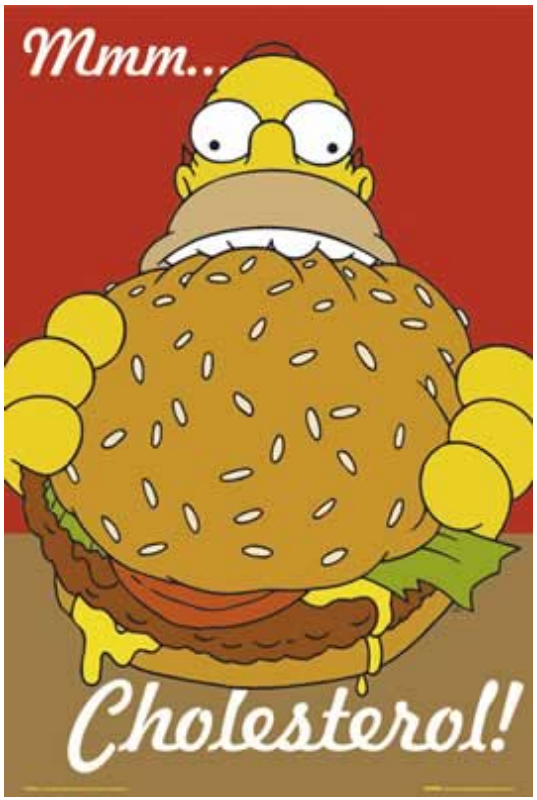
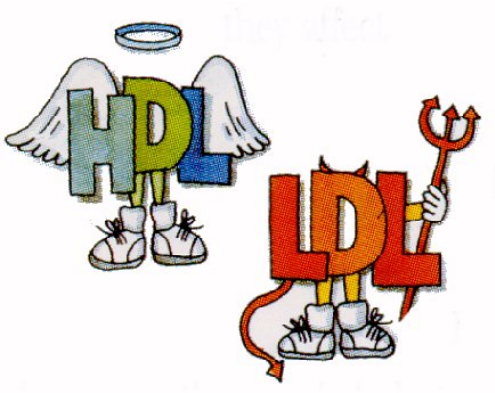
GENES REGULATING CHOLESTEROL METABOLISM

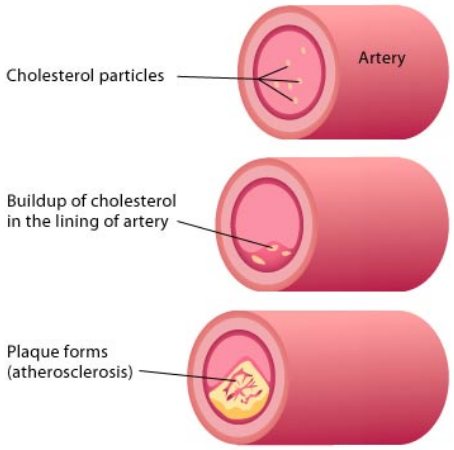


Chau Vu
Bio 118

Functions of Cholesterol

- Maintain membrane fluidity, facilitate trafficking and signaling of membrane-associated proteins
- Precursor for important metabolites
- LDL = low density lipoprotein
- HDL = high density lipoprotein
- High LDL → atherosclerosis

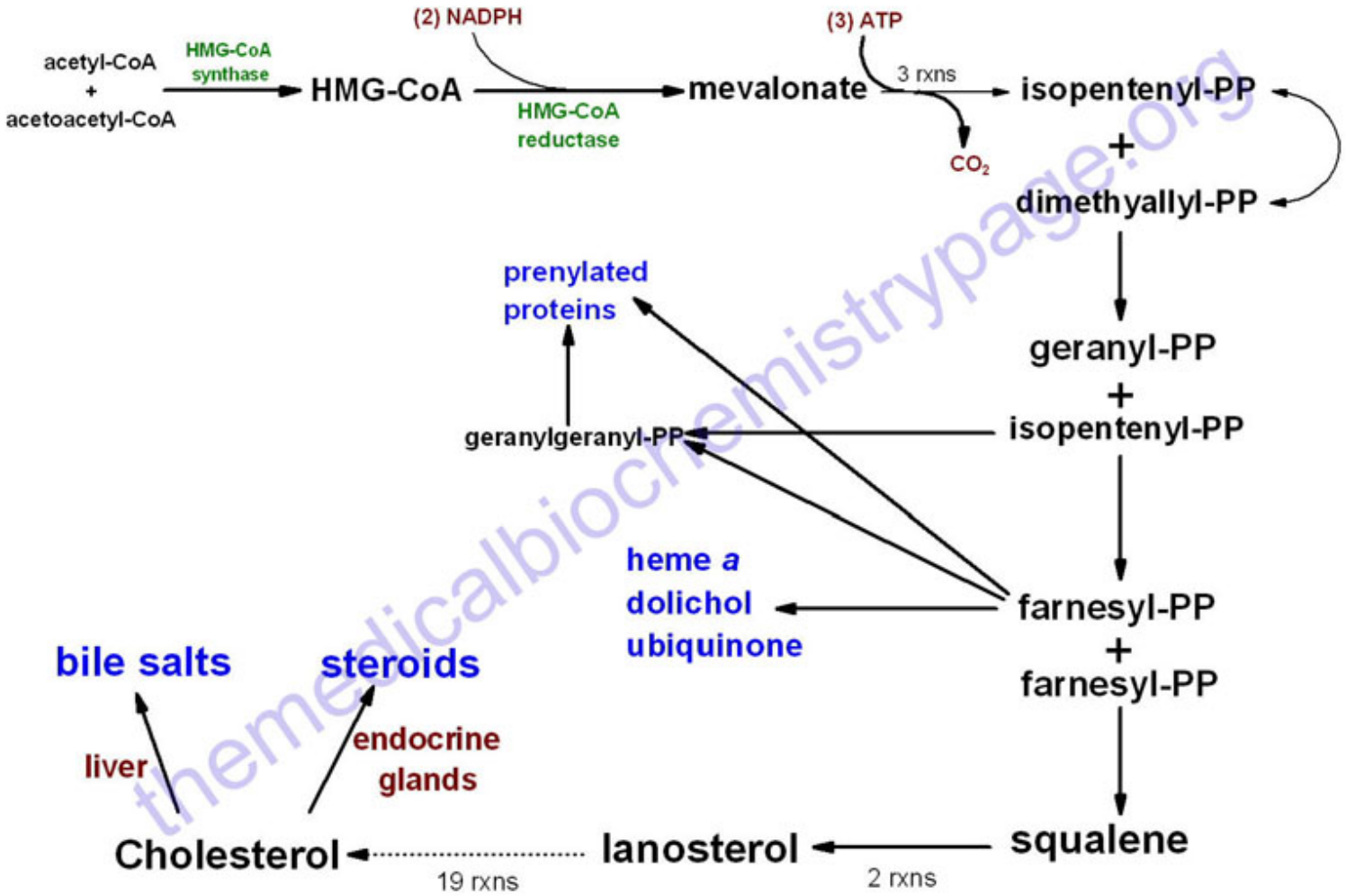




Synthesis of cholesterol

- Occurs in cytoplasm and microsomes
- acetyl-CoA – starting material
- Less than half from biosynthesis *de novo*
  - liver 10%
  - intestines 15%
- 5 major steps

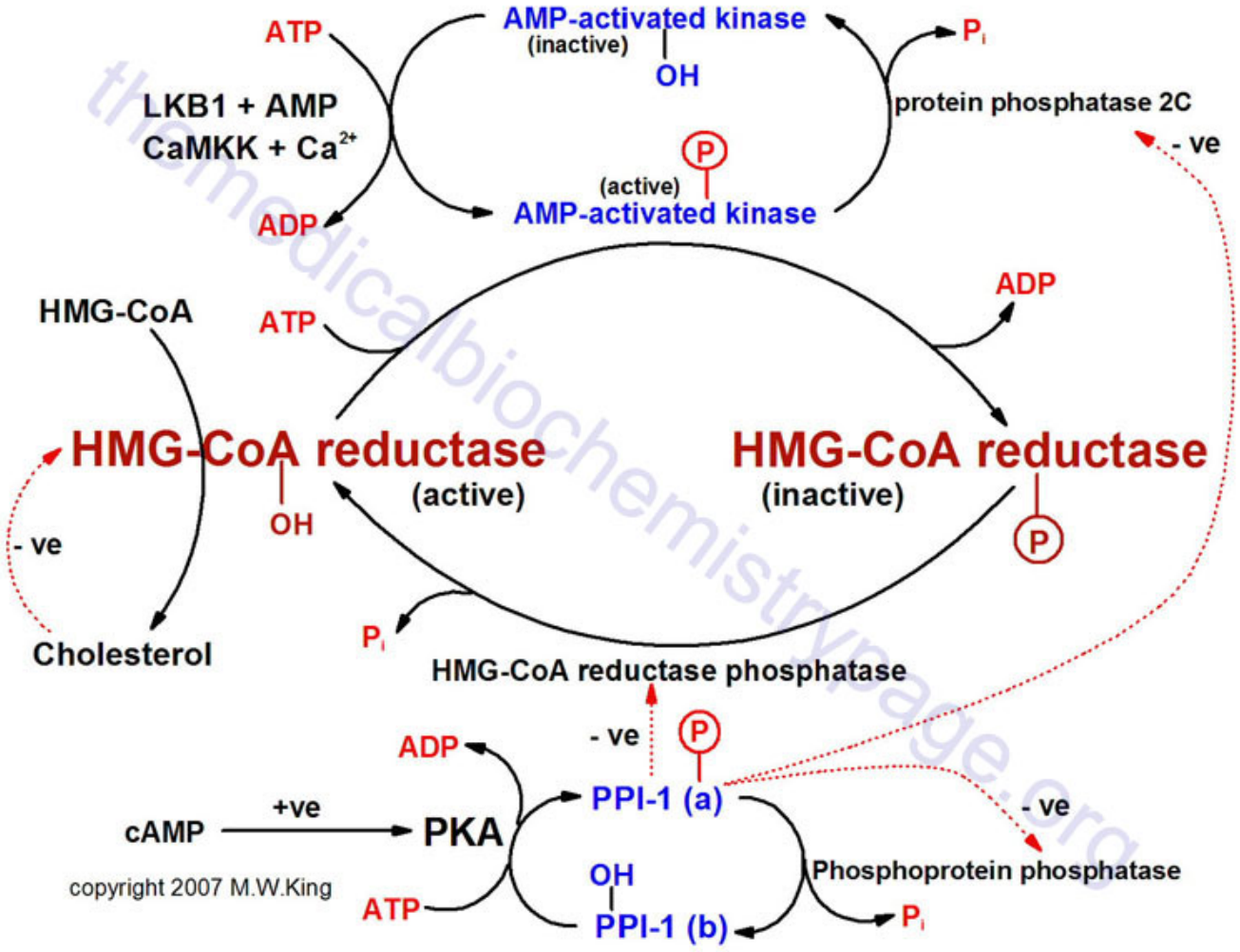
SYNTHESIS OF CHOLESTEROL



Regulation of cholesterol

- Synthesis and dietary intake:
  - Normal Adult: produce1g/day; consume 0.3g/day
- Pathway 1: LDL binds to receptors; receptor-ligand complex absorbed by endocytosis
- Pathway 2: cholesterol synthesized when intra-cellular levels are low
- Pathway 3: reduce HMG CoA reductase activity; excess cholesterol transported to the liver
- Involve many transcription factors, binding proteins, enzymes and receptors

REGULATION OF CHOLESTEROL SYNTHESIS

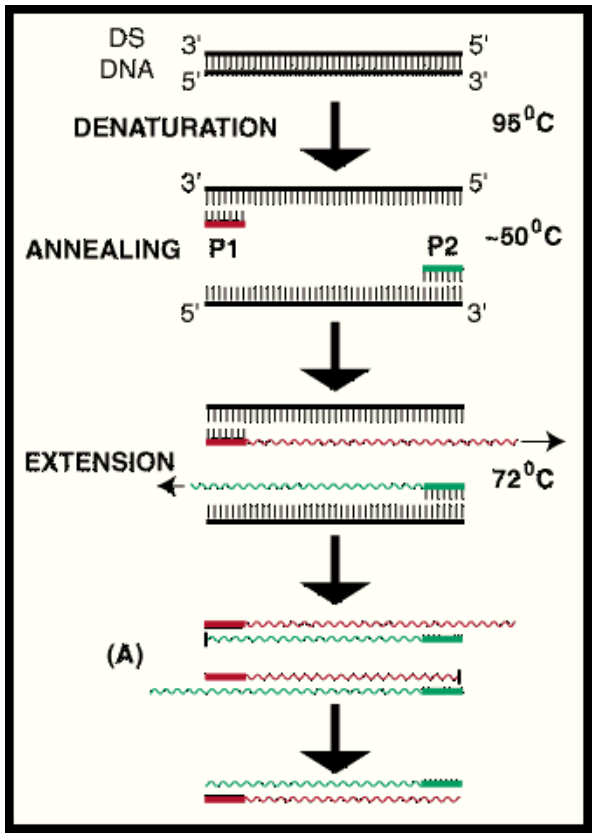


GAPS IN OUR UNDERSTANDING OF CHOLESTEROL METABOLISM

- Heritability of human plasma cholesterol levels ~ 50% to 70%.
- Known common genetic factors linked to cholesterol explain 5 to 7% of heritability
- common polymorphisms that modulate plasma cholesterol levels account for small portion

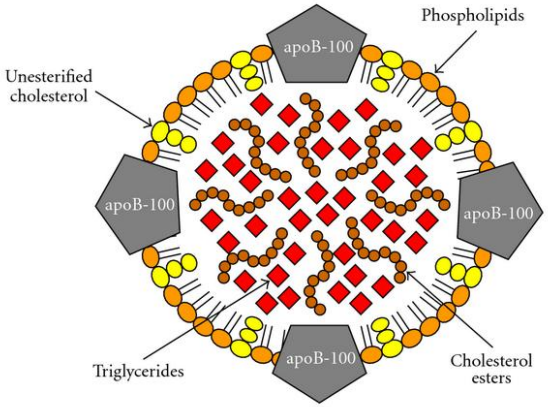
Study 1: Changes in the expression of cholesterol metabolism-associated genes in HCV-infected liver

- real time PCR
- Results
  - (SREBP)-2 expression unchanged
    - transcription protein, induces production of sterols; negative feedback loop
  - low density lipoprotein receptor expression reduced by 90% in HCV infected liver
    - mediates endocytosis of LDL(cholesterol)



Study 1: Changes in the expression of cholesterol metabolism-associated genes in HCV-infected liver

- Expression of apolipoprotein B100, microsomal triglyceride transfer protein and ABC G5 transporter significantly increased
  - Apolipoprotein B100 - protein the binds to LDL; carry LDL to tissue
  - Microsomal Triglyceride transfer protein - helps produce beta-lipoproteins
  - ATP-binding cassette G5; proteins limits intestinal absorption and promotes biliary excretion of sterols



Study 1: Changes in the expression of cholesterol metabolism-associated genes in HCV-infected liver

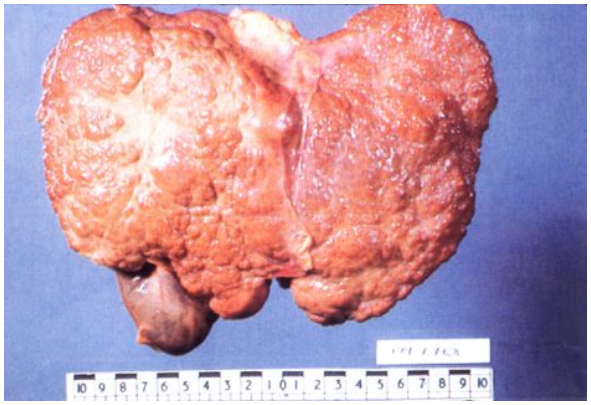
- Up-regulation of HMG-CoA reductase, HMG-CoA synthase and squalene synthase
  - HMG-CoA reductase- rate controlling enzyme for the mevalonate pathway
  - HMG-CoA synthase - enzyme that catalyzes production of HMG-CoA
  - Squalene synthase - enzyme for sterol synthesis
  - Confirmed enhanced de novo cholesterol synthesis

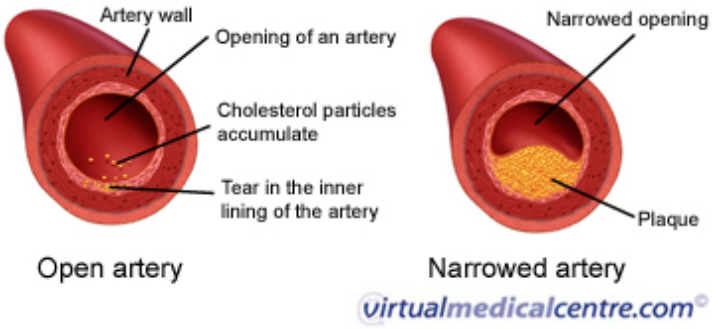
Study 1: Changes in the expression of cholesterol metabolism-associated genes in HCV-infected liver

- Expression of *cholesterol* 7alpha-hydroxylase and farnesoid X receptor enhanced
- bile salt export pump expression was unchanged.
  - Cholesterol 7 alpha-hydroxylase – enzyme in rate limiting step of bile acids, converts cholesterol to 7-alpha-hydroxycholesterol
  - Farnesoid X receptor- suppression of *cholesterol* 7alpha-hydroxylase (CYP7A1), rate-limiting enzyme in bile acid synthesis cholesterol.

Study 1: Changes in the expression of cholesterol metabolism-associated genes in HCV-infected liver

- Conclusions:
  - regulation of lipid metabolism impaired
  - cholesterol and fatty acid synthesis increase without negative feedback





GWAS STUDIES

- Six new loci associated with blood LDL, HDL or triglycerides in humans
  - large sample sizes, multiple cohorts
  - common SNPs at 18 loci associated with concentrations LDL, HDL, and/or triglycerides.
  - Six of the 18 loci are new
    - Two LDL (1p13 near *CELSR2, PSRC1* and *SORT1* and 19p13 near *CILP2* and *PBX4*)
    - one HDL cholesterol (1q42 in *GALNT2*)
    - five triglycerides (7q11 near *TBL2* and *MLXIPL*, 8q24 near *TRIB1*, 1q42 in *GALNT2*, 19p13 near *CILP2* and *PBX4* and 1p31 near *ANGPTL3*).

GWAS STUDY

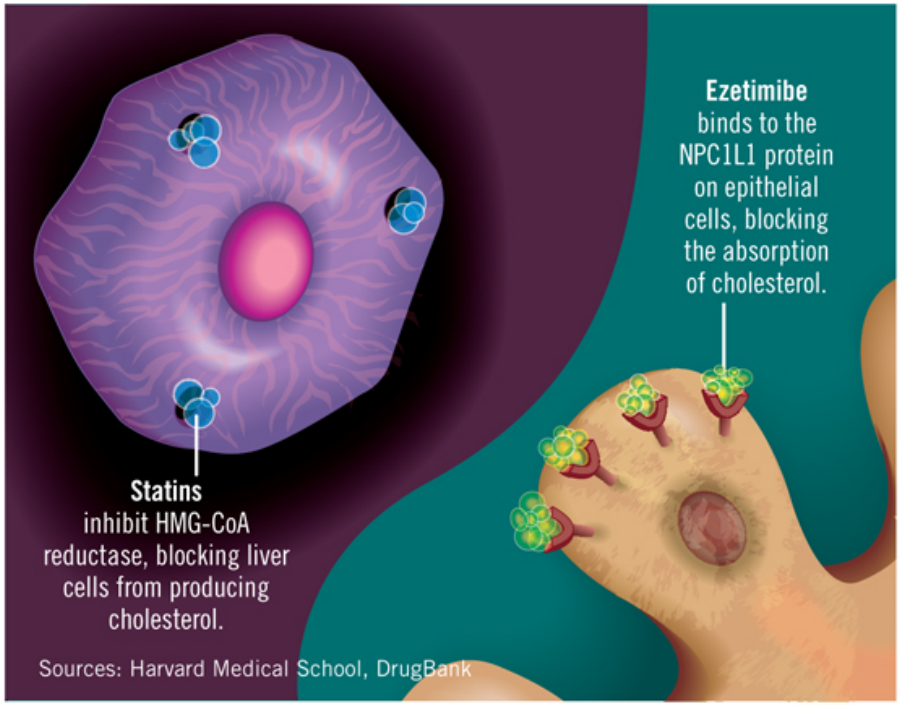
- Common variants at 30 loci contribute to polygenic dyslipidemia
  - The 11 newly defined loci
    - LDL near *ABCG8*, *MAFB*, *HNF1A* and *TIMD4*
    - HDL cholesterol near *ANGPTL4*, *FADS1-FADS2-FADS3*, *HNF4A*, *LCAT*, *PLTP* and *TTC39B*
    - triglycerides near *AMAC1L2*, *FADS1-FADS2-FADS3* and *PLTP*.
  - proportion of individuals with high LDL cholesterol, low HDL cholesterol and high triglycerides varied according to allelic dosage score
  - cumulative effect; contributes to polygenic dyslipidemia

How these findings will affect the treatment of CVD: the case of FH

- caused by mutations in *LDLR* gene
  - apolipoprotein B-100 gene (APOB)
  - proprotein convertase subtilisin/kexin type 9 gene (PCSK9)
- over 700 variants
- reduced number of functional LDL receptors
- severe elevation of plasma LDL cholesterol levels
- FH responds well to drug treatment, early diagnosis to reduce atherosclerosis risk
- new factor identified → potential new target for therapy

Novel Therapy: Update on Patented Cholesterol Absorption Inhibitor

- Statins: block the rate determining step in the biosynthesis of cholesterol
- Ezetimibe: inhibit cholesterol absorption
- Combination therapy of ezetimibe and statins
- Newer analogues under clinical trials, among which darapladib, FM-VP4 and A-002



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