GENES REGULATING CHOLESTEROL METABOLISM

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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 $\rightarrow$ 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

1. acetyl-CoA + acetoacetyl-CoA \xrightarrow{\text{HMG-CoA synthase}} \text{HMG-CoA}
2. HMG-CoA \xrightarrow{\text{HMG-CoA reductase}} \text{mevalonate}
3. \text{mevalonate} \xrightarrow{3 \text{rxns}} \text{isopentenyl-PP} + \text{dimethylallyl-PP}

\text{isopentenyl-PP} + \text{dimethylallyl-PP} \xrightarrow{\text{geranyl-PP}} \text{geranylglycerol-PP}
\text{geranylglycerol-PP} \xrightarrow{\text{2 rxns}} \text{squalene}

\text{Cholesterol} \xrightarrow{19 \text{rxns}} \text{lanosterol} \xrightarrow{2 \text{rxns}} \text{heme, dolichol, ubiquinone
Regulation of Cholesterol

- Synthesis and dietary intake:
  - Normal Adult: produce 1g/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 7alpha-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 MLXIP1, 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
BIBLIOGRAPHY


