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Cholesterol

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1. Know the general pathway for cholesterol biosynthesis.
    a. All carbons are derived from acetate
    b. Cytosolic
    c. Mechanism
        i. Thiolase:Acetyl-CoA Acetyltransferase: 2 Acetyl-CoA --> Acetoacetyl-CoA + CoASH
        ii. HMG-CoA Synthase: Acetoacetyl-CoA + Acetyl-CoA --> HMG-CoA + CoASH
        iii. HMG-CoA Reductase: HMG-CoA + 2 NADPH --> Mevalonate + 2 NADP+ + CoA
        iv. Mevalonate --> Squalene
        v. Squalene --> Lenosterol
        vi. Lenosterol --> Cholesterol
2. Know the major site of regulation. --> HMG-CoA Reductase
3. Know how HMG-CoA Reductase is regulated.
    a. Long term feedback control of amount of enzyme
        i. Decrease in cholesterol concentration --> release of ER membrane protein
        ii. Sterol Regulatory Element-Binding Protein and SREBP Cleaveage Activating Protein bound together on ER membrane
        iii. Sterol levels decline and complex migrate to Golgi
        iv. Two cleavages result in SREBP migrating to nucleus
        v. Transcription of HMG-CoA reductase and LDL receptor gene
        vi. Due to this system, dietary cholesterol control alone does not necessarily work because you just produce more cholesterol
    b. Covalent Modification
        i. Activated by dephosphorylation by PPP
            1) Insulin activates PPP
            2) Glucagon --> PKA --> AMP Kinase --> phosphorylates/inactivates HMG CoA Reductase
        ii. Statins are competitive inhibitors of HMG CoA Reductase