**Lecture #11**

Lecture 11
2/27/04

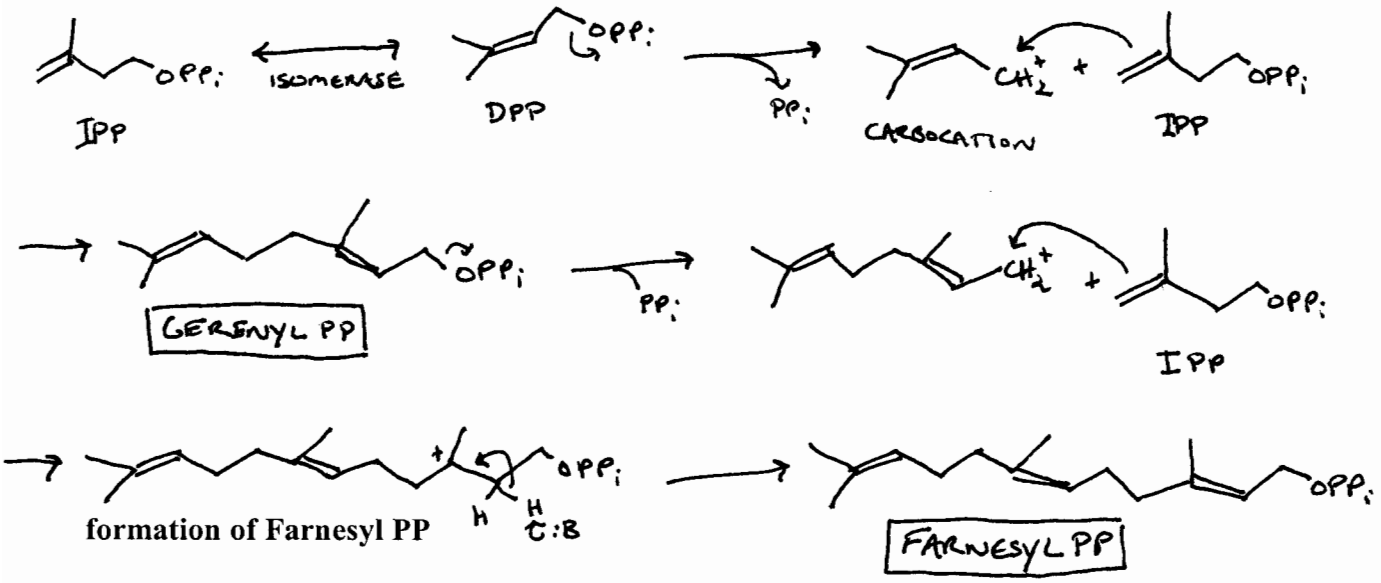
Cholesterol (abbrev here as Ch)
-biosynthesis
-regulation, homeostasis
-sensing insoluble molecules

Ch is made into bile acids in 15-20 steps (hydroxylation via heme dependent enzymes)
How do you balance making Ch versus obtaining it from your diet?

Handout 2A page 2
-biosynthesis pathway (origin of carbons)
- conversion of mevalonate to IPP via decarboxylative elimination
(IPP is a precursor to hundreds of natural products)
**NOTE**: remember when you have ATP, you almost always have $Mg^{2+}$ around – neutralizes the negative charges on the phosphate groups, allows nucleophilic attack

IPP-> DAPP via an isomerase
Loss of PPi to give carbocation intermediate
Condense with IPP to add 5 carbon units, forms tertiary carbocation, which subsequent to loss of a proton generates geranylPP ($C_{10}$)

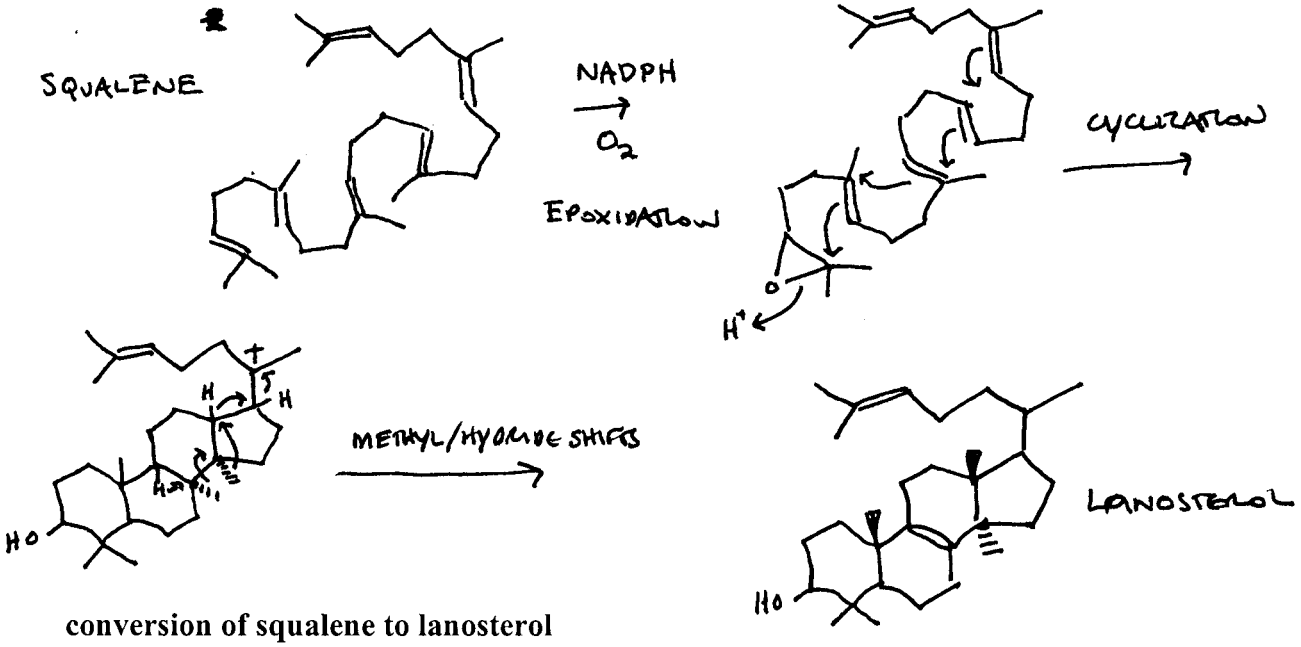
Generanyl PP loses PPi to give carbocation and IPP adds to given a carbocation which then deprotonates to form farnesyl PP ($C_{15}$)
Farnesyl PP is a central player, involved in many pathways (see handout 2d page 1)
100's of natural products from FPP
-i.e. TERPENES – major constituents of perfumes
all proteins that make terpenes are structurally homologous



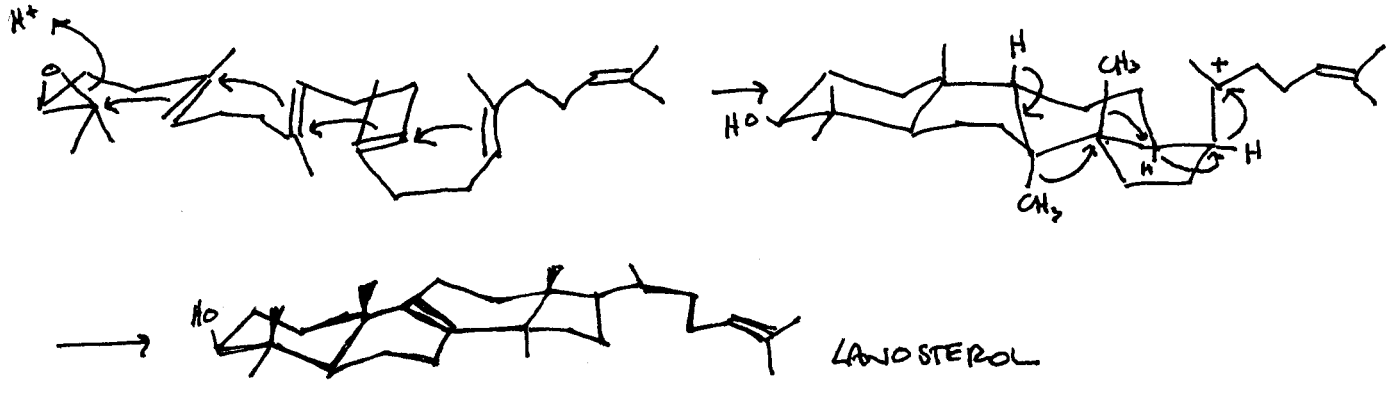

**formation of Farnesyl PP**

Formation of Squalene
2FPP-> Squalene ($C_{30}$) via squalene synthase and NADPH

squalene synthase is a regulatory point in the pathway




**conversion of squalene to lanosterol**
(first epoxidize squalene by squalene epoxidase, ring opening of the epoxide triggers the cyclization to generate a cation which is quenched by methyl and hydride shifts and ultimately a deprotonation. Stereoelectronic control is the key to which hydrides and methyl anions migrate.
pi-cation interaction from an appropriately placed aromatic side chain of an amino acid in a specific location within the active site allows you to do only the desired chemistry The position of the aromatic ring of the amino acid side chain stabilizes selectively certain carbonium ions.




stereochemical view of cyclization
Lanesterol-> several steps-> Cholesterol

Brown and Goldstein- Trends in Cell Biology (2003)

2 types of regulation
-LDL receptor, receptor mediatd endocytosis
-Sterol responsive element binding protein

Overview of Questions
Ch homeostasis
-regulate whether to make Ch or obtain from the diet
page 5 of handout 2d - body levels of Ch
most endogenous biosynthesis of Ch occurs in the liver
Ch in plasma is insoluble on its own, must be somehow packaged into appropriate lipoprotein particles to be soluble

LIVER (Bodies central metabolic clearing house) – maintains the appropriate levels of nutrients for the muscle and brain, adipose tissues
ADIPOCYTES -> Fat storage (fats provide a more efficient way to store energy than sugars)

Page 7 of handout2d (see also page 4 for nomenclature and abbreviations)
Overview of cholesterol and lipid homeostasis

In the cytosol of liver cells
ACoA -> MCoA (via acetyl CoA carboxylase (ACC))
MCoA-> palmitate-> TAG

ACoA-> HMGCoA-> mevalonate(via HMGCoA reductase- regulated)->
Squalene (via regulated squalene synthase)-> cholesterol

VLDL = Very Low Density Lipoprotein
Packages TAG and Ch, carries these insoluble metabolites in the blood

TAG transported to adipocytes, Lipase on the surface of the adiposities hydrolyzes TAG to Fatty acids to bring FA into adipocyte, FA is then converted back to TAG, the major storage form.
When needed, another lipase(regulated by the appropriate protein kinase) returns TAG to FAs for use and transported back to blood albumin

Intestine brings in TAG and Ch from diet

Bile acids excreted from liver in bile, transferred to intestine and help solubilize TAG and Ch. Bile acids are detergents or emulsifiers and help to solubilize these insoluble materials. In the intestine TAGs and Ch and protein are converted to chylomicrons (CM) and transported via blood to liver

How do you sense Ch and whether you have enough from your diet?