Chapter 9 LIPID BIOSYNTHESIS

Biosynthesis of Fatty Acids and Eicosanoids

Long-chain saturated fatty acids are synthesized from acetyl-CoA by a cytosolic complex of six enzyme activities plus acyl carrier protein (ACP).

Fatty acid biosynthesis and breakdown occur by different pathways, are catalyzed by different sets of enzymes, and take place in different parts of the cell. Moreover, biosynthesis requires the participation of a three-carbon intermediate, malonyl-CoA.

Malonyl-CoA Is Formed from Acetyl-CoA and Bicarbonate

Fatty Acid Synthesis Proceeds in a Repeating Reaction Sequence

Six more molecules of malonyl-ACP react successively at the carboxyl end of the growing fatty acid chain to form palmitoyl-ACP—the end product of the fatty acid synthase reaction. Free palmitate is released by hydrolysis

Biosynthesis of Triacylglycerols

Triacylglycerols and Glycerophospholipids Are Synthesized from the Same Precursors

Showing the required shapes and formulas on the board

Triacylglycerol Biosynthesis in Animals Is Regulated by Hormones

Biosynthesis of Membrane Phospholipids

Diacylglycerols are the principal precursors of glycerophospholipids.

In bacteria, phosphatidylserine is formed by the condensation of serine with CDP-diacylglycerol; decarboxylation of phosphatidylserine produces phosphatidylethanolamine.

Phosphatidylglycerol is formed by condensation of CDP-diacylglycerol with glycerol 3-phosphate, followed by removal of the phosphate in monoester linkage.

Phospholipids travel to their intracellular destinations via transport vesicles or specific proteins.

Biosynthesis of Cholesterol, Steroids, and Isoprenoids

The steroid hormones (glucocorticoids, mineralocorticoids, and sex hormones) are produced from cholesterol by alteration of the side chain and introduction of oxygen atoms into the steroid ring system.

Cholesterol is an essential molecule in many animals, including humans. Cholesterol has a crucial role as a component of cellular membranes. It is also precursor of steroid hormones and bile acids.

But it is not required in the mammalian diet—all cells can synthesize it from simple precursors. Much of the cholesterol synthesis in vertebrates takes place in the liver.

Cholesterol Is Made from Acetyl-CoA in Four Stages

1. In addition to cholesterol, a wide variety of isoprenoid compounds are derived from mevalonate.
2. Conversion of mevalonate to activated isoprene units;
3. Polymerization of six 5-carbon isoprene units to form the 30-carbon linear squalene; and
4. cyclization of squalene to form the four rings of the steroid nucleus, with a further series of changes (oxidations, removal or migration of methyl groups) to produce cholesterol

Cholesterol Has Several Fates

A small fraction of the cholesterol made there is incorporated into the membranes of hepatocytes, but most of it is exported in one of three forms: biliary cholesterol, bile acids, or cholesteryl esters.

All growing animal tissues need cholesterol for membrane synthesis, and some organs (adrenal gland and gonads, for example) use cholesterol as a precursor for steroid hormone production. Cholesterol

Cholesterol Biosynthesis Is Regulated at Several Levels

In mammals, cholesterol production is regulated by intracellular cholesterol concentration and by the hormones glucagon and insulin. The rate-limiting step in the pathway to cholesterol (and a major site of regulation) is the conversion of HMGCoA to mevalonate.

Cholesterol synthesis is also inhibited by elevated concentrations of intracellular cholesterol, which acts through covalent modification and transcriptionalregulation mechanisms.

Cholesterol and Other Lipids Are Carried on Plasma Lipoproteins

Cholesterol and cholesteryl esters, like triacylglycerols and phospholipids, are essentially insoluble in water, yet must be moved from the tissue of origin to the tissues in which they will be stored or consumed. They are carried in the blood plasma as plasma lipoproteins, macromolecular complexes of specific carrier proteins, **apolipoproteins,** with various combinations of phospholipids, cholesterol, cholesteryl esters, and triacylglycerols.

Cholesterol and cholesteryl esters are carried in the blood as plasma lipoproteins. VLDL carries cholesterol, cholesteryl esters, and triacylglycerols from the liver to other tissues, where the triacylglycerols are degraded by lipoprotein lipase, converting VLDL to LDL.

Cholesteryl Esters Enter Cells by Receptor-Mediated Endocytosis