What is Lipid Biosynthesis?

Lipids are important for energy storage, membrane integrity, hormones, signaling, and numerous other biological functions. Lipids come in several forms including fatty acids, triglycerides, phospholipids, and cholesterol.

Overview

Lipids come in several forms including those that are generated by distinct biosynthetic pathways:

- Fatty acids
- Triglycerides
- Phospholipids
- Sterols

Fatty acids are long chain hydrocarbons synthesized by the iterative addition of malonyl-CoA to an acyl chain on an acyl carrier protein. This process is carried out by the enzymes acetyl-CoA carboxylase (ACCase) and fatty acid synthase (FAS). FAS enzymes come in two forms: (1) FAS I is a multi-enzyme complex primarily found in mammals, fungi, and plants, and (2) FAS II is a series of separate enzymes that recapitulate the enzymatic activities of the FAS I complex and are primarily found in bacteria and several parasitic protozoa. Fatty acids are important building blocks for more complex lipids.

Triglycerides (or triacylglycerols) and phospholipids are the primary fate of fatty acids. Triglycerides are a major form of energy storage while phospholipids are a major component of lipid membranes. A variety of triglycerides and phospholipids with different functions and fates can be produced depending on the fatty acids that are incorporated and the enzymatic pathways utilized.

Cholesterol is a lipid that is synthesized in the liver, transported in the bloodstream, and used in the construction of cell membranes in animals. Ergosterol is the fungal equivalent to cholesterol. These and other sterols use acetyl-CoA as a primary building block. Synthesis of cholesterol and ergosterol involves more than 20 steps and a variety of enzymes including: mevalonate pathway, isoprenoid pathway, condensation of isoprene to squalene, and cyclization of squalene to lanosterol. Lanosterol can then be converted to cholesterol (animals), stigmasterol (plants) or ergosterol (fungi and several parasitic protozoa).

Existing Products

There are numerous lipid biosynthesis inhibitors that are approved or in late stage clinical development for a variety of diseases.
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<th>Lipid Biosynthetic Pathway</th>
<th>Target Name</th>
<th>Development Status</th>
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<td>Melvonate pathway</td>
<td>HMGCoA reductase</td>
<td>Multiple Statins, FDA approved for lowering LDL-cholesterol</td>
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<td>Lanosterol conversion to ergosterol</td>
<td>CYP51</td>
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<td>Fatty acid synthesis</td>
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**Lipid Biosynthesis Inhibitors as Non-Neglected Tropical Disease Therapeutics**

There are several diseases that are not related to neglected tropical diseases for which lipid biosynthesis has been targeted, including atherosclerosis/heart disease and fungal infections.

Statins are inhibitors of the enzyme HMGCoA reductase, a key biosynthetic enzyme in the melvonate pathway that is utilized for the production of cholesterol in humans. High levels of low density lipoprotein (LDL)-cholesterol can lead to the formation of fatty plaques in the arteries, also known as atherosclerosis, and eventually heart disease. HMGCoA reductase inhibitors are the cornerstone for the treatment of high LDL-cholesterol and several products have demonstrated the ability to prevent heart attack and stroke as a result of their effects on LDL-cholesterol.

Fungi produce ergosterol as a primary sterol. This is in contrast to humans and other mammals that produce primarily cholesterol. Although fungi that infect humans may salvage some cholesterol from the host, this is not sufficient to replace de novo ergosterol biosynthesis. The enzyme C14alpha-demethylase (CYP51) is involved in both ergosterol and cholesterol biosynthesis. Inhibitors of CYP51 have been used successfully to treat invasive fungal infections in humans. Although CYP51 inhibitors may also inhibit some cholesterol biosynthesis in humans, they do not significantly decrease cholesterol levels since the majority of human cholesterol comes from diet rather than de novo synthesis.

**Lipid Biosynthesis Inhibitors as Neglected Tropical Disease Therapeutics**

Lipid biosynthesis has been targeted for antibacterial development due to differences between bacterial and mammalian fatty acid biosynthesis. Mycolic acids are long chain fatty acids that are unique to the cell wall of a group of bacteria that includes *Mycobacterium tuberculosis*, the bacterium that causes human tuberculosis. *M. tuberculosis* is particularly interesting because it uses both FAS I and FAS II pathways to produce mycolic acids. Isoniazid (INH) is the cornerstone of first line tuberculosis treatment. INH inhibits an enzyme in the *M. tuberculosis* FAS II pathway InhA, an enoyl acyl carrier protein reductase. Inhibition of InhA interferes with the synthesis of the mycobacterial cell wall. Pyrazinamide (PZA) inhibits the *M. tuberculosis* FAS I pathway and is used as part of combination therapies with INH and rifampicin for the treatment of tuberculosis.
The success of FAS I and II inhibitors for the treatment of tuberculosis suggests exploitation of differences in fatty acid and other lipid biosynthetic pathways between mammalian, bacterial, and parasitic organisms is a viable strategy for future neglected tropical disease drug development.

References