Therapeutic Opportunities and Challenges for Lipogenesis Inhibitor Development

Fatty acids are essential for cell survival and function as biological energy substrates, structural components, and signaling molecules. Given their critical role, cells have evolved mechanisms to produce fatty acids from alternative carbon sources, through a process called de novo lipogenesis (DNL).

Although DNL is essential for maintaining systemic and intracellular environmental stability, its chronic elevation is associated with the development of a variety of diseases and disorders, including cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), type 2 diabetes (T2D), multiple cancers, viral infections, autoimmune diseases, and neurodegeneration. Therefore, inhibition of DNL's core enzymes, including citrate/isocitrate carriers (CIC), ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACC), and fatty acid synthase (FAS), becomes a very attractive therapeutic strategy.

Currently, a variety of natural products of DNL inhibitors have been discovered. Some of these compounds are in clinical development and have been approved for the treatment of hyperlipidemia, or are in advanced development in NAFLD and oncology.

Citrate/isocitrate carrier (CIC)

Structurally, eukaryotic CIC consists of three homologous domains, each of which forms two hydrophobic transmembrane alpha-helices connected by hydrophilic rings, and at least two citric acid binding sites, located at different locations in the transmembrane region, serve as CIC inhibitor binding sites.

CTPI-2 is a new-generation competitive CIC inhibitor with a 20-fold increase in affinity over first-generation CPI-1 and can inhibit citrate transport at lower concentrations. CIC expression is increased in the liver of NASH patients. CPI-2 treatment can reverse steatohepatitis and liver damage in HFD-fed mice while reducing serum cholesterol and triglycerides. Inhibition of CIC may have beneficial effects on obesity, NAFLD, and T2D as well. In addition, CIC has become an attractive target for anticancer drug development. This is because its expression is increased in several cancer cells and inhibition of CIC slows cell growth.

ATP citrate lyase (ACLY)

The first discovered and widely studied ACLY inhibitor is (−)-hydroxycitric acid (HCA), a citric acid derivative found in tropical plants like garcinia and hibiscus. In addition, several synthetic inhibitors based on targeted strategies are designed to disrupt the formation of stable citryl-CoA intermediates that bind to the active site.

MEDICA 16 is one of the earliest synthesized ACLY inhibitors that resemble fatty acids. It reduces liver lipid content, liver glucose production, and improves peripheral insulin sensitivity in several different models of obesity-induced insulin-resistant rodents. In addition, early studies in animal models demonstrated a broad range of lipid-lowering effects of MEDICA 16 on circulating cholesterol and triglyceride levels, as well as related beneficial effects on vascular and cardiomyopathy.

Acetyl-CoA carboxylase (ACC)

Inhibition of ACC reduces malonyl-CoA, which is also an allosteric inhibitor of carnitine palmitoyltransferase I, a rate-limiting enzyme that controls the passage of fatty acids into mitochondria for beta-oxidation. Therefore, ACC inhibition is an effective method for simultaneously inhibiting DNL and increasing fatty acid oxidation.

Currently, a number of ACC inhibitors have entered human clinical trials. Pfizer developed

PF-05221304 as a selective, orally bioavailable, and reversible ACC inhibitor that is preferentially distributed to the liver, thereby avoiding potential toxicity associated with the inhibition of platelet formation and developmental defects. In the Phase II clinical trial of NAFLD, PF-05221304 reduced liver fat by up to 65% in a dose-dependent way and decreased HbA1c at the highest dose.

Fatty acid synthase (FAS)

Several new small-molecule FAS inhibitors have been developed that inhibit the TE domain. Orlistat, also known as tetrahydro leptin, is a derivative of leptin that inhibits FAS by irreversibly binding to the TE domain. FAS inhibitors targeting the KR domain have also been developed, with a few entering clinical trials, including GSK's GSK2194069, Boehringer Ingelheim's BI-99179, and TVB-3166 & TVB-2640 designed by Sagimet Biosciences.

Success and challenges

Over the past decade, lipogenesis inhibitors have entered clinical development in cancer, cardiovascular disease, NASH, and other diseases. However, the balance between efficacy and safety is an urgent issue for DNL inhibitor development in the future, as enhanced potency may lead to increased compensatory upregulation or toxicity.

Ultimately, whether DNL inhibitors are safe and effective enough to be used as monotherapy, or will be used in combination with other therapies, will depend on clinical trials. In this regard, the results of studies on the ACLY inhibitor phenylpropionic acid are encouraging, which suggest that chronic suppression of DNL in the liver is safe when administered alone or in conjunction with other standards of care. It also gives us more confidence in developing DNL inhibitors, which could be the basis for a novel category of treatment.