

Findings on sphingolipid biosynthesis may lead to new treatments for metabolic diseases

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Almost all cell types exhibit some sort of polarity, which enables them to carry out specialized functions. Adherens junctions, which consist of the transmembrane protein cadherin and the intracellular components beta-catenin, alpha-catenin, and actin filaments, initiate cell-cell contacts and maintenance of cell polarity. Because all cell membranes that define cell boundaries and polarity contain lipid bi-layer structures, the lipid, including sphingolipid, environment could influence polarity, yet the mechanism underlying this remission is unknown.

Now, research led by SUNY Downstate Medical Center shows that blockage of sphingolipid de novo synthesis pathway (through knockout Serine Palmitoyltransferase, the key enzyme in the pathway) impairs hepatocyte polarity, attenuates liver regeneration after hepatectomy, and promotes tumorigenesis. Importantly, the deficiency significantly reduces sphingomyelin but not other sphingolipids in hepatocyte plasma membrane, and greatly reduces cadherin, the major protein in adherens junctions, on the membrane. The deficiency affects cellular distribution of b-catenin, the central component of the canonical Wnt pathway.

Furthermore, such a defect can be partially corrected by sphingomyelin supplementation in vivo and in vitro. SUNY Downstate's Professor of Cell Biology Xian-Cheng Jiang, PhD, and Assistant Professor of Surgery Chongmin Huan, MD, PhD, are co-corresponding authors of the article detailing the research.

Dr. Jiang explained, "This was a seven-year effort and a breakthrough

linking sphingolipid-mediated cell junctions and tumorigenesis. Our results, for the first time, show that plasma membrane sphingomyelin-related b-catenin cellular distribution is one the key factors in regulating hepatocyte polarity and tumorigenesis."

Dr. Jiang concludes, "This study also will provide a guide for the development of serine palmitoyltransferase inhibitors, which have a potential for the treatment of metabolic diseases such as diabetes."

More information: Zhiqiang Li et al, Liver Serine Palmitoyltransferase (SPT) Activity Deficiency in Early Life Impairs Adherens Junctions and Promotes Tumorigenesis, *Hepatology* (2016). DOI: [10.1002/hep.28845](https://doi.org/10.1002/hep.28845)

Provided by SUNY Downstate Medical Center

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