Current Research in Lipids

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Lipid Research Division Seminar Series

Wednesdays | 12 p.m. EST

Weekly presentations from young researchers highlighting their recent work in the field of lipids. Hosted by the ASBMB's Lipid Research Division.

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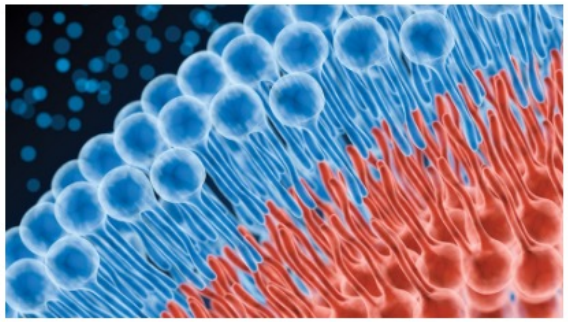

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RESEARCH ARTICLE

Last step in the path of LDL cholesterol from lysosome to plasma membrane to ER is governed by phosphatidylserine

Michael Trinh
Graduate Student

Michael N. Trinh, Michael S. Brown, Joseph L. Goldstein, Jaeil Han, Gonçalo Vale, Jeffrey G. McDonald, Joachim Seemann, Joshua T. Mendell, and Feiran Lu

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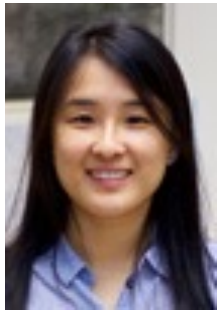
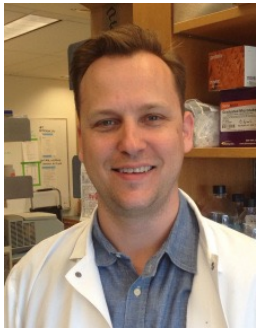
Contributed by Joseph L. Goldstein, June 17, 2020 (sent for review May 27, 2020; reviewed by Ta-Yuan Chang and Stephen G. Young)



Feiran Lu
Principal Investigator

Significance

Feedback control of cholesterol metabolism is essential for cell viability and prevention of heart attacks. Cells acquire cholesterol from receptor-mediated uptake of low-density lipoprotein, which delivers cholesterol to lysosomes. To exert feedback control, cholesterol must reach the endoplasmic reticulum (ER). Here we use a CRISPR screen to show that lysosome-derived cholesterol moves first to the plasma membrane and then to the ER. The last movement requires an enzyme that produces phosphatidylserine. This demonstrates that transmembrane movement of one lipid (cholesterol) requires another lipid (phosphatidylserine). Our results explain how one organelle (ER) monitors the cholesterol content of another organelle (plasma membrane), thereby maintaining membrane integrity and ensuring cell survival.



Jason Correnti, Ph.D.
Postdoctoral Research Fellow

Liver-specific ceramide reduction alleviates steatosis and insulin resistance in alcohol-fed mice[S]

Jason Correnti*, Chelsea Lin*, Jascha Brettschneider*, Amy Kuriakose*, Sookyoung Jeon*, Eleonora Scorletti*, Amanke Oranu†, Dru McIver-Jenkins*, Isabelle Kaneza*, Delfin Buyco*, Yedidya Saiman*, Emma E. Furth§, Josepmaria Argemi**, Ramon Bataller**, William L. Holland†† and Rotonya M. Carr[1,*]

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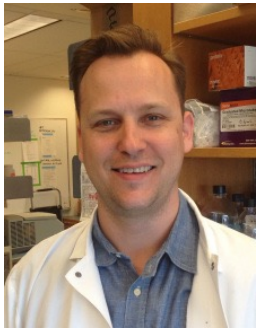
ABSTRACT

Alcohol's impairment of both hepatic lipid metabolism and insulin resistance (IR) are key drivers of alcoholic steatosis, the initial stage of alcoholic liver disease (ALD). Pharmacologic reduction of lipotoxic ceramide prevents alcoholic steatosis and glucose intolerance in mice, but potential off-target effects limit its strategic utility. Here, we employed a hepatic-specific acid ceramidase (ASAH) overexpression model to reduce hepatic ceramides in a Lieber-DeCarli model of experimental alcoholic steatosis. We examined effects of alcohol on hepatic lipid metabolism, body composition, energy homeostasis, and insulin sensitivity as measured by hyperinsulinemic-euglycemic clamp. Our results demonstrate that hepatic ceramide reduction ameliorates the effects of alcohol on hepatic lipid droplet (LD) accumulation by promoting VLDL secretion and lipophagy, the latter of which involves ceramide cross-talk between the lysosomal and LD compartments. We additionally demonstrate that hepatic ceramide reduction prevents alcohol's inhibition of hepatic insulin signaling. These effects on the liver are associated with a reduction in oxidative stress markers and are relevant to humans, as we observe peri- LD ASAH expression in human ALD. Together, our results suggest a potential role for hepatic ceramide inhibition in preventing ALD.

Rotonya M. Carr, MD
Principal Investigator



Jason Correnti, Ph.D.
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Rotonya M. Carr, MD
Principal Investigator

Hepatic ceramides are increased in ALD patients (13), and we and others have demonstrated that long-chain hepatic ceramides are increased in ALD rodent models (8, 9, 13–17). Ceramides are synthesized via three major pathways: *1*) de novo synthesis resulting from the condensation of serine and palmitate in the ER by the pathway's rate limiting enzyme, serine palmitoyl transferase; *2*) lysosomal salvage due to the reacylation of sphingosine derived from more complex sphingolipids; and *3*) sphingomyelin hydrolysis. We recently established that ceramides are present in the LD fraction and regulate *Plin2* gene transcription through the enzyme ceramide synthase (10), whose activity is required for both ER de novo and lysosomal ceramide synthesis. Lysosomal ceramides can be subsequently deacylated into the ceramide precursor, sphingosine, by ceramidases.