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SEMINAR

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הנושא

Hither and yon - a lysosome-dependent lipid degradative mechanism in liver cells treated with omega-3 fatty acids

Tuesday, September 2, 2014, 9:30
Faculty Club
Robert H. Smith Faculty of Agriculture, Food and Environment, Rehovot, the Hebrew University of Jerusalem

Pharmacological dosage of ω-3 fatty acids, such as eicosapentaenoic acid (EPA, 20:5n-3), has been shown to exert a beneficial effect in ameliorating hypertriglyceridemia and nonalcoholic fatty liver disease. However, cellular mechanisms by which ω-3 fatty acids could lower triglycerides both in the plasma and in the liver are unclear. In lipid-laden liver cells, triglycerides are present as cytosolic droplets in cell periphery. Treatment of the cells with EPA results in rapid lipid turnover, involving a direct interaction of lysosomes with the droplets, a process that does not require Atg5- or Atg8-dependent autophagocytosis. The EPA-triggered lipid turnover is achieved through redistribution of lysosomes from perinucler region to cell periphery, which is accompanied with lysosomal acidification. Robust kiss-and-run between lysosomes and droplets, analogues to the process associated with endosome maturation, requires anterograde and retrograde motility of lysosomes. Thus, depletion of RILP or FYCO1 (two Rab7 effectors), or depolymerizing microtubules, effectively abolishes the EPA-triggered lipid degradation. EPA also induces association of Rab5 and Rab7 with the droplets, and depletion of Rab5 or Rab7 completely blocks EPA-triggered lipid turnover. Moreover, overexpression of Arl8b markedly accelerates lipid degradation. Depletion of Arl8b entirely abolishes the EPA action. These data suggest that ω-3 fatty acid treatment results in accelerated lipid degradation regulated by a group of small GTPases. Our finding reveals a novel ω-3 fatty acid-triggered, lysosome-dependent lipid degradation pathway in liver cells, and offers an explanation for the therapeutic benefits of ω-3 fatty acids in preventing and treatment of hepatosteatosis associated with nonalcoholic fatty liver disease.

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