

Cell Homeostasis or Cell Death—The Balancing Act Between Autophagy and Apoptosis Caused by Steatosis-Induced Endoplasmic Reticulum (ER) Stress

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Abstract

Metabolic-dysfunction-associated steatotic liver disease (MASLD) is a prevalent liver condition with potential progression to cirrhosis and impaired regeneration post-resection. A key mechanism underlying lipotoxicity is endoplasmic reticulum (ER) stress, particularly the activation of the unfolded protein response (UPR). This study investigates the interplay between lipid accumulation, endoplasmic reticulum (ER) stress, and cellular outcomes, focusing on the balance between autophagy and apoptosis. We cultured primary human hepatocytes (PHH) in a free fatty acid (FFA)-enriched medium for 120 h, assessing lipid accumulation, metabolism, and the expression of selected UPR markers. Additionally, we investigated the effects of lipid load on cell activity and growth in proliferating HepG2 cells. We observed that FFA uptake consistently induced ER stress, shifting cellular responses toward apoptosis under high lipid loads. Donor-specific differences were evident, particularly in lipid storage, excretion, and sensitivity to lipotoxicity. Some donors exhibited limited triglyceride (TAG) storage and excretion, leading to an excess of FFA whose metabolic fate remains unclear. Proliferation was more sensitive to lipid accumulation than overall cell activity, with even low FFA concentrations impairing growth, highlighting the vulnerability of regenerative processes to steatosis. The study elucidates how ER stress pathways, such as PERK-CHOP and IRE1 α -JNK, are differentially activated in response to lipid overload, tipping the balance toward apoptosis in severe cases. The limited activation of repair mechanisms, such as autophagy, further emphasizes the critical role of ER stress in determining hepatocyte fate. The donor-dependent variability highlights the need for personalized strategies to mitigate lipotoxic effects and enhance liver regeneration in steatosis-related conditions.