Comparative Gene Identification-58 (CGI-58)-deficiency in Mice: Evidence for a Major Role of CGI-58 in Acylceramide Formation

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Efficient triacylglycerol (TG) hydrolysis by adipose triglyceride lipase (ATGL) requires CGI-58. In contrast to ATGL mutations in human and ATGL deficiency in mice, mutations of CGI-58 in humans are associated with ichthyosis. The phenotypical difference in neutral lipid storage disease (NLSD) caused by CGI-58 mutations indicates an ATGL-independent function of CGI-58. In this study, we generated and characterized mice lacking CGI-58. CGI-58-deficient mice developed NLSD with severe ichthyosis leading to postnatal death within 12 to 16 hours after birth. The loss of CGI-58 was associated with reduced epidermal TG hydrolase activity and differential skin lipid composition. Strikingly, newborn CGI-58-deficient mice exhibited negligible levels of epidermal acylceramides, which crucially affected skin permeability. Importantly, these changes were not observed in newborn ATGL-deficient mice. All together, our findings demonstrate that CGI-58 activates the epidermal TG catabolism, which is essential for acylceramide synthesis.