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Total Sphingomyelin Synthase Activity Deficiency Results in Lipodystrophy

Sphingomyelin (SM) is a vital sphingolipid abundant in cell plasma membranes, crucial for cell structure, signaling, and membrane integrity. Two isoforms, SMS1 and SMS2, of the sphingomyelin synthase (SMS) family catalyze SM formation from ceramide and phosphatidylcholines (PCs). Our preliminary findings indicate adipose tissues express both isoforms, with SMS1 being predominant. Although literature indicate that SMS1 deficiency from birth or SMS2 deficiency resulted in reduction of adipose tissue mass with varying degrees, single deficiency of SMS1 or SMS2 is not sufficient to examine the effect of SM reduction on adipocyte metabolism. Here we hypothesize that total SM synthase activity deficiency could result in lipodystrophy by regulating adipogenesis, lipogenesis, and/or lipolysis. We established two mouse models : global inducible SMS1 knockout (sKO) and global SMS2 knockout/ global inducible SMS1 knockout (dKO) to investigate the impact of SMS KO in adulthood. Strikingly, while sKO mice only showed adipose tissue reduction only under high-fat diet, dKO exhibited lipodystrophy under chow diet(CD) . Decreased PPAR γ 2, FASN, and CD36 protein levels, alongside unchanged ATGL in sKO mice under CD, suggest SM deficiency may impede adipogenesis and lipogenesis. Our study aims to elucidate the impact and underlying mechanism of total SM synthase deficiency on adipocyte metabolism, offering novel insights into obesity treatment strategies.