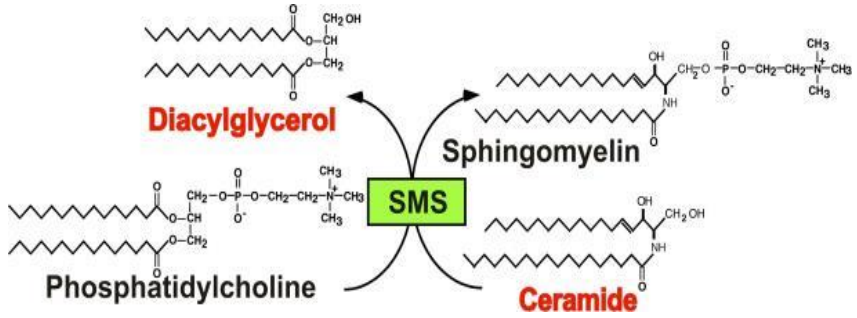
Sphingomyelin Synthase 1 Plays a Crucial Role in Non-Alcoholic Fatty Liver Disease

A. Pettey, G. Deevska, A. Karakashian, M. Nikolova-Karakashian

Alex Pettey, Lab Tech Sr

Introduction:

Excess accumulation of fat in hepatocytes (steatosis) is a hallmark of NAFLD and is caused by deregulation of lipid metabolism. Offsetting the metabolism of Ceramide and DAG, two key bioactive lipids, is considered a culprit for the onset and progression of NAFLD. Sphingomyelin synthase (SMS) is the sole enzyme with the capacity to regulate the homeostasis of both, DAG and Ceramide, but its function in NAFLD is unclear. SMS exists in three forms, (SMS1,2 and R) and the Golgi localized SMS1 is the major form.



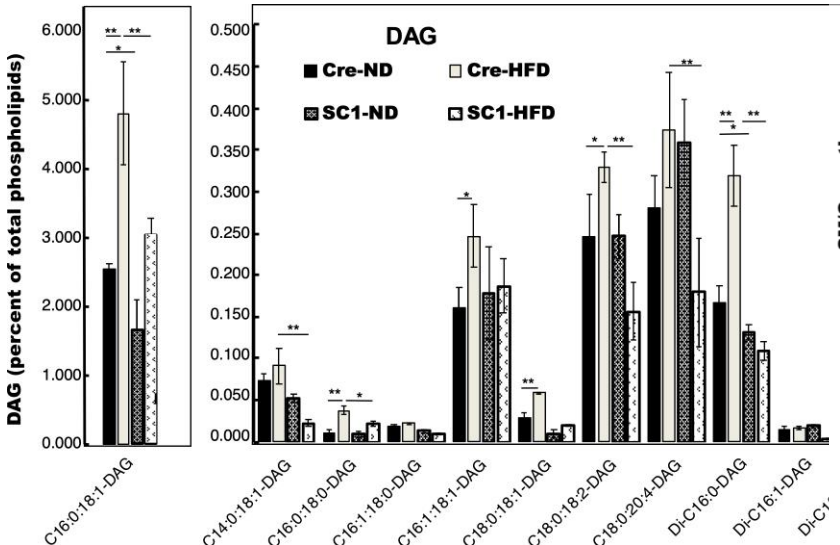
Experimental design

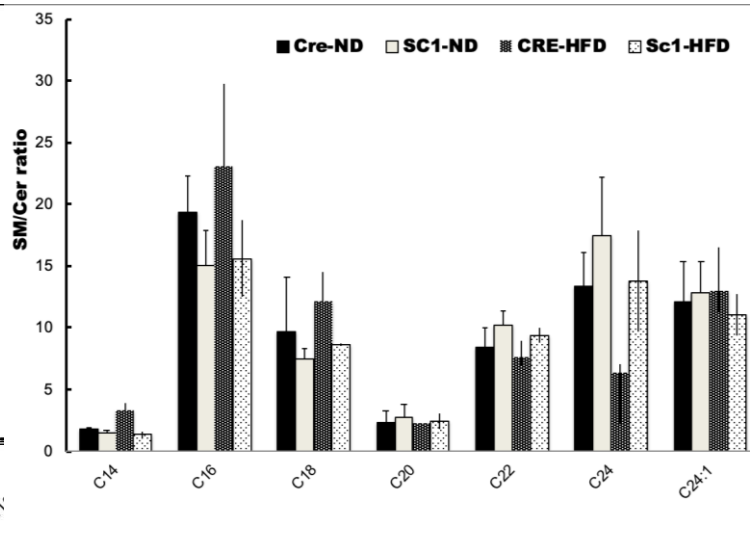
Mice: Cre mice (AlbCre+/+): SC1 mice (Sgms1fl/fl, AlbCre+/+ mice)

Diet: High fat (65%, HFD); Methionine/Choline Deficient (MCD); Control: ND

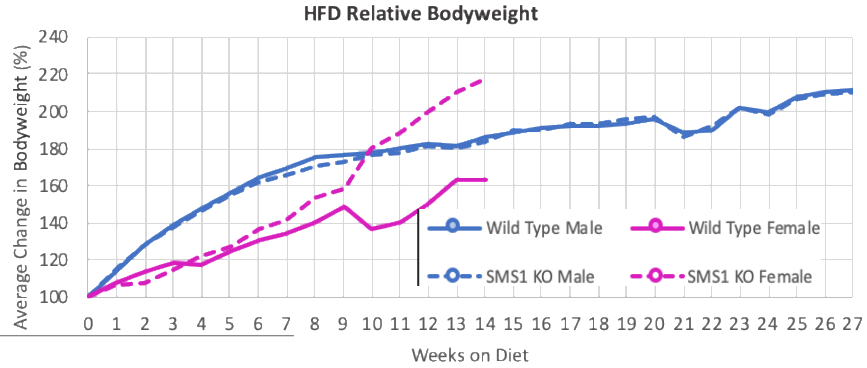
Results:

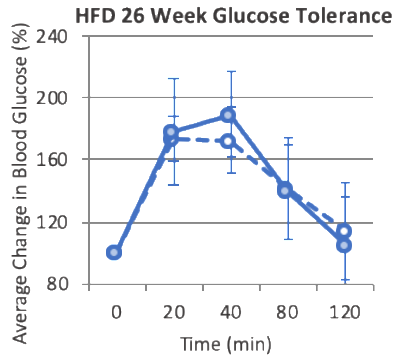
1. SMS1 regulates DAG and ceramide levels during obesity-associated NAFLD

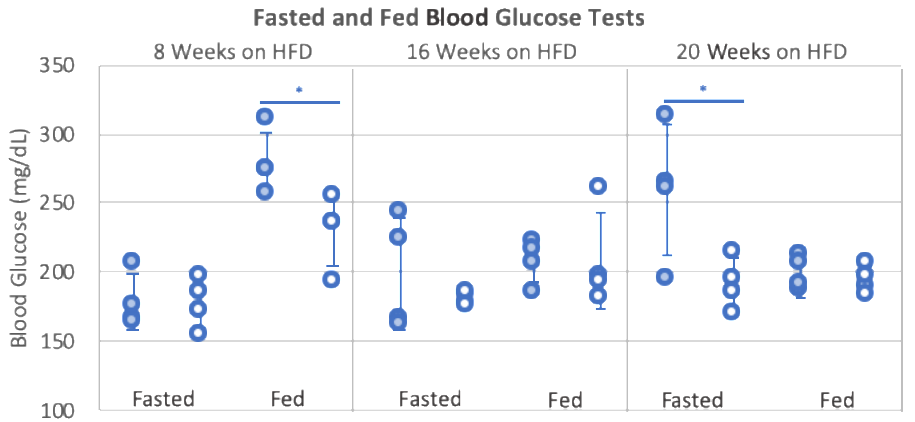




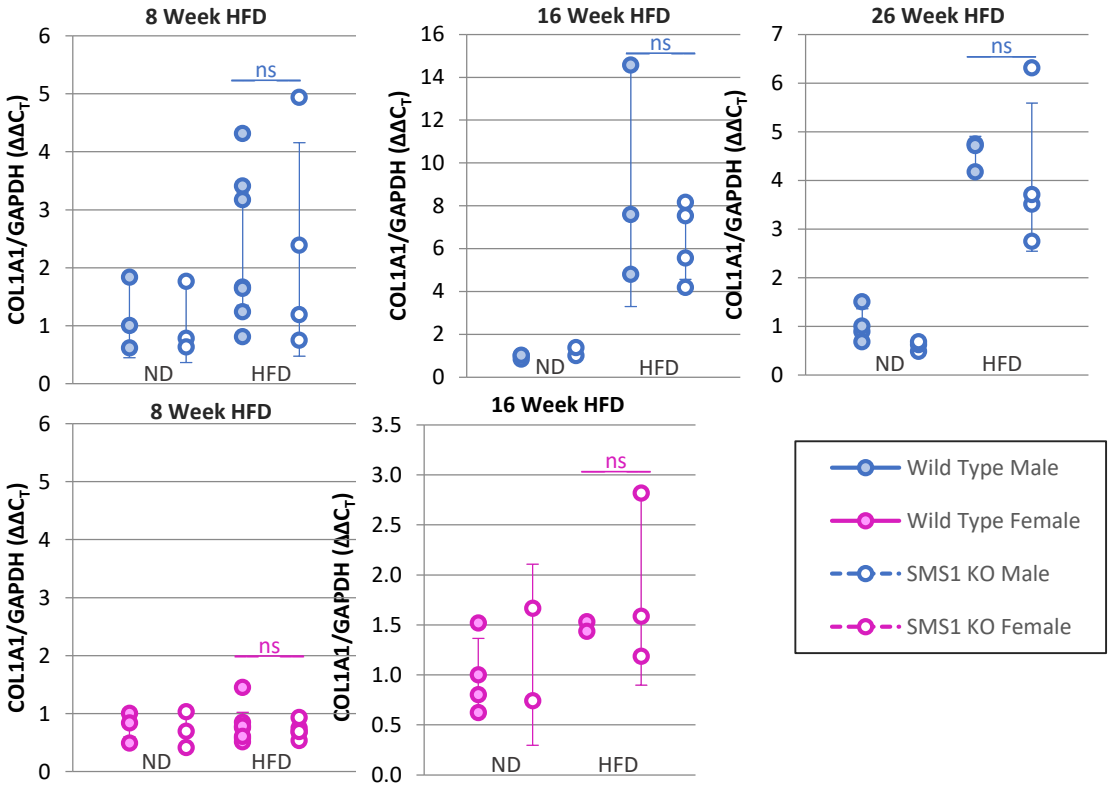
2. SMS1 deletion has no effect on body weight gain and delays the onset of insuin resistance

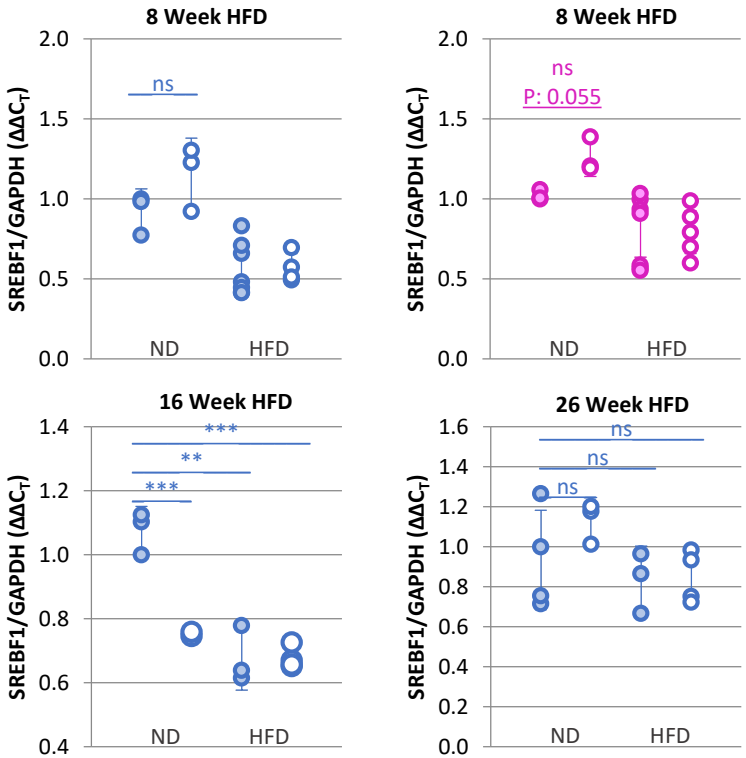


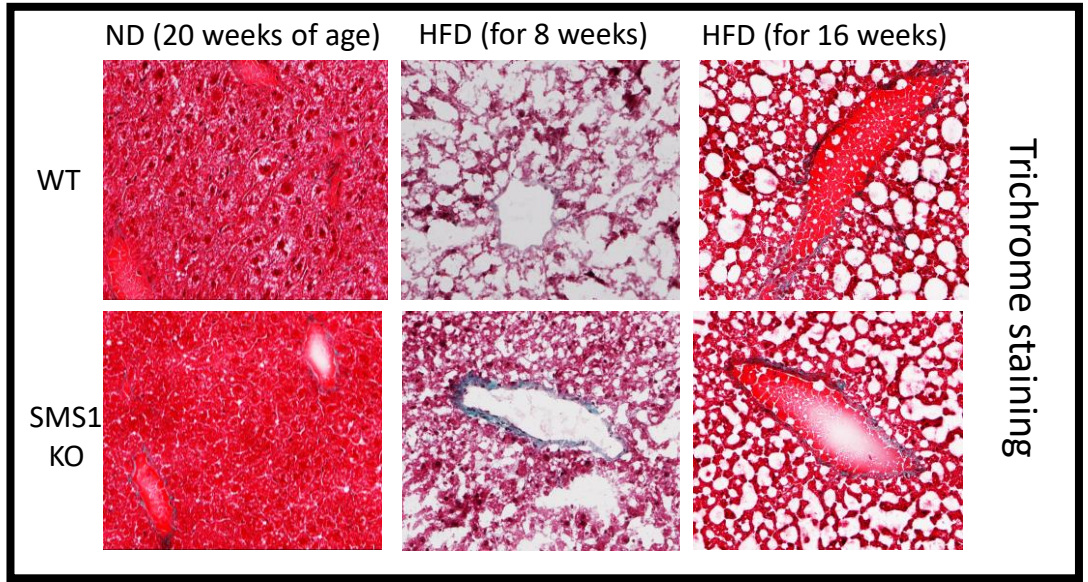


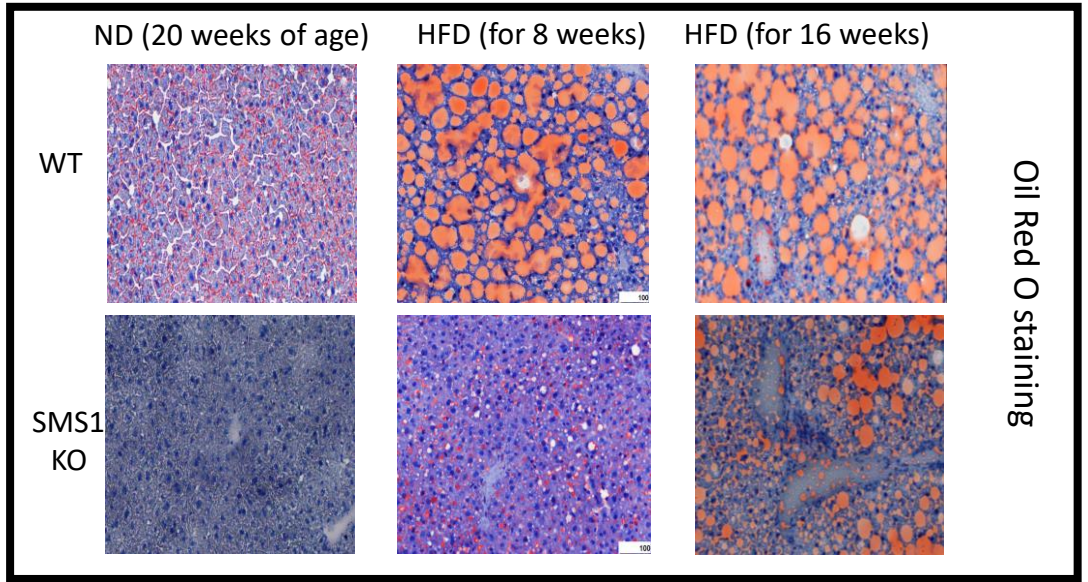


3. SMS1 Deletion Suppresses de novo Lipogenesis in the Liver Based on SREBF1 mRNA Level and Histology

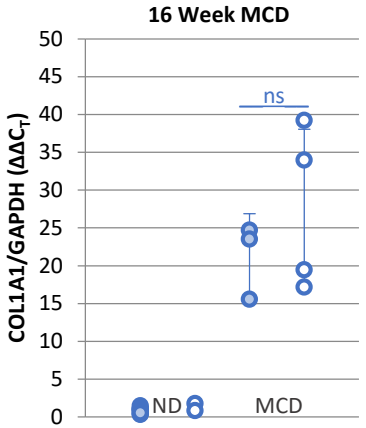


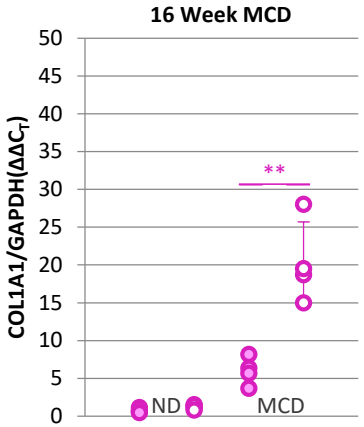


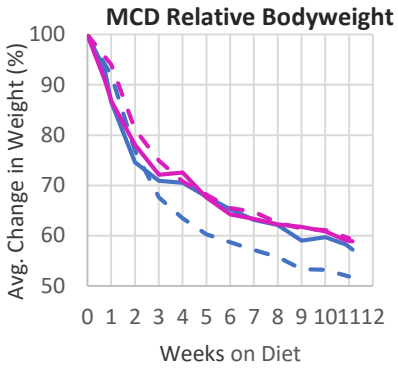


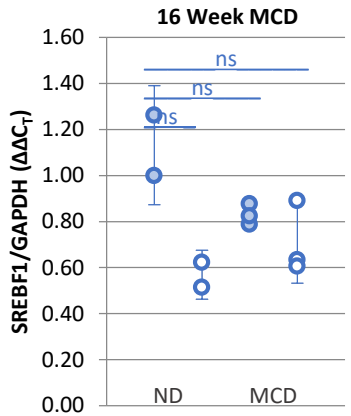


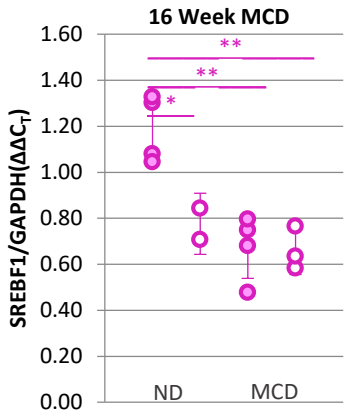
4. MCD Diet Exacerbates NAFLD Phenotypes in SMS1 KO Mice

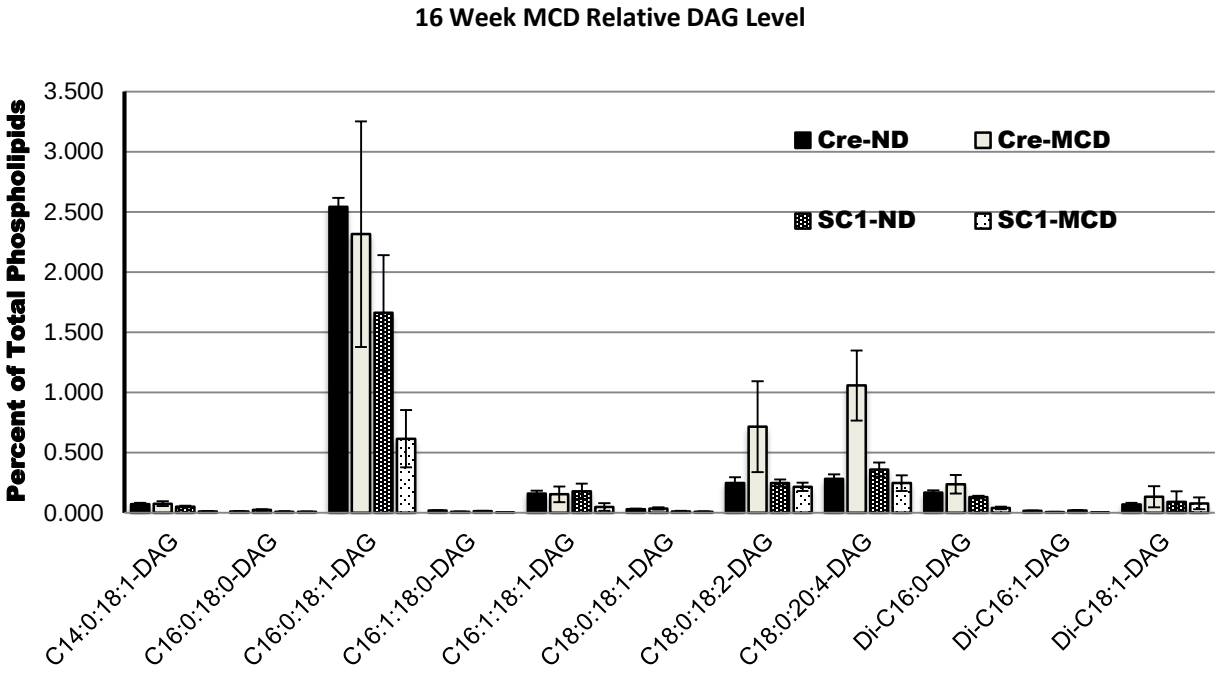


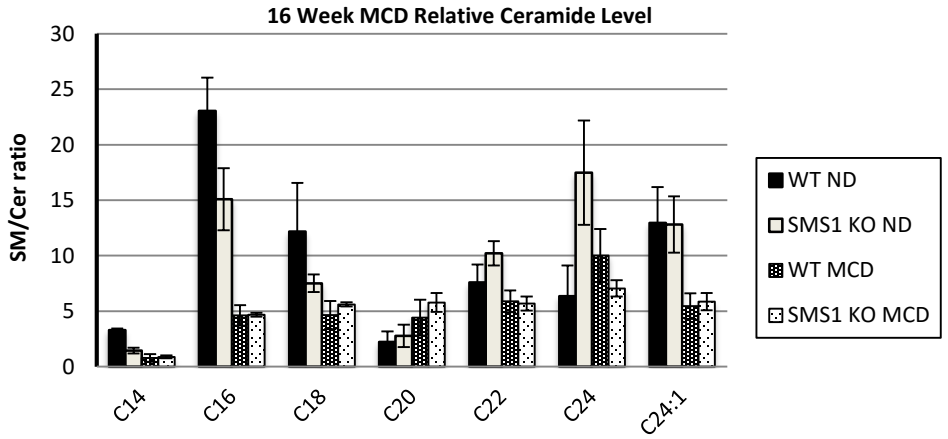












Conclusions:

1. SMS1 regulates the levels not only of SM and ceramide but those of DAG.
2. De novo lipogenesis is suppressed in SMS1 deficient mice.
3. HFD-induced DAG accumulation is significantly alleviated by SMS1 deletion.
4. SMS1 deficiency is linked to the appearance of spontaneous fibrosis.
5. SMS1 deficient mice show delayed insulin resistance when placed on HFD, and defective lipogenesis, resulting in a decreased steatotic phenotype.