

Table S8. Experimentally studies linking metabolite levels to T2DM pathophysiology.

Reference	Metabolites	Organism	Source	Phenotypic observation
Koves et al. [1]	Citrate; L-Malate; Fumarate; L-Lactate; 2-Oxoglutarate	Rodent	Muscle	Lower amounts of organic acids were found in obese diabetic rats compared to the lean diabetic rats
Salek et al. [2]	L-Leucine; Pyruvate; Citrate; beta-Alanine; D-Alanine; L-Alanine	Human	Urine	Increased amounts in T2DM
	L-Malate;, L-Glutamate; Fumarate; Phosphocreatine			Decreased amounts in T2DM
Ellis et al [3] Ye et al [4]	Palmitoyl-CoA; Tetradecanoyl-CoA; Palmitoleoyl-CoA; Decanoyl-CoA; Lauroyl-CoA	Human/Rodent	Muscle	Strong negative correlation between insulin sensitivity and the content of LC-CoA (Ellis et al) Fall of glucose uptake into muscle was accompanied by increase in plasma TG and muscle LC-CoA (Ye et al)
Chavez et al [5]	1,2 -Diacyl-sn-glycerol (DAG); Palmitoyl-CoA; Palmitoleoyl-CoA	Rodent tissue culture	Adipocytes/myotubes	Palmitate induced the accrual of ceramide and diacylglycerol (DAG), two lipid metabolites inhibit insulin signaling in cultured cells
Neschen et al [6]	Glycerol -3-phosphate; glycerol	Rodent	Liver	Suppression of mitochondrial GPAT1 (TG synthesis) activity results in lowered DAG and reversal of hepatic insulin resistance
Yu et al. [7]	1,2 -Diacyl-sn-glycerol (DAG); Palmitoyl-CoA; Palmitoleoyl-CoA	Rodent	Muscle	Accumulation of DAG and other bioactive lipid molecules is thought to engage stress-activated serine kinases that interfere with insulin signal transduction
Holland et all [8]	Palmitoleoyl-CoA	Rodent	Liver	Inhibition of ceramide synthesis protected rodents against insulin resistance induced by infusion of saturated fatty acid

References

1. Koves TR, Ussher JR, Noland RC, Slentz D, Mosedale M, et al. (2008) Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. *Cell Metab* 7: 45-56.
2. Salek RM, Maguire ML, Bentley E, Rubtsov DV, Hough T, et al. (2007) A metabolomic comparison of urinary changes in type 2 diabetes in mouse, rat, and human. *Physiol Genomics* 29: 99-108.
3. Ellis BA, Poynten A, Lowy AJ, Furler SM, Chisholm DJ, et al. (2000) Long-chain acyl-CoA esters as indicators of lipid metabolism and insulin sensitivity in rat and human muscle. *Am J Physiol Endocrinol Metab* 279: E554-560.
4. Ye JM, Doyle PJ, Iglesias MA, Watson DG, Cooney GJ, et al. (2001) Peroxisome proliferator-activated receptor (PPAR)-alpha activation lowers muscle lipids and improves insulin sensitivity in high fat-fed rats: comparison with PPAR-gamma activation. *Diabetes* 50: 411-417.
5. Chavez JA, Summers SA (2003) Characterizing the effects of saturated fatty acids on insulin signaling and ceramide and diacylglycerol accumulation in 3T3-L1 adipocytes and C2C12 myotubes. *Arch Biochem Biophys* 419: 101-109.
6. Neschen S, Morino K, Hammond LE, Zhang D, Liu ZX, et al. (2005) Prevention of hepatic steatosis and hepatic insulin resistance in mitochondrial acyl-CoA:glycerol-sn-3-phosphate acyltransferase 1 knockout mice. *Cell Metab* 2: 55-65.
7. Yu C, Chen Y, Cline GW, Zhang D, Zong H, et al. (2002) Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate-1 (IRS-1)-associated phosphatidylinositol 3-kinase activity in muscle. *J Biol Chem* 277: 50230-50236.
8. Holland WL, Brozinick JT, Wang LP, Hawkins ED, Sargent KM, et al. (2007) Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance. *Cell Metab* 5: 167-179.