Targeting the AMPK pathway for the treatment of Type 2 diabetes.

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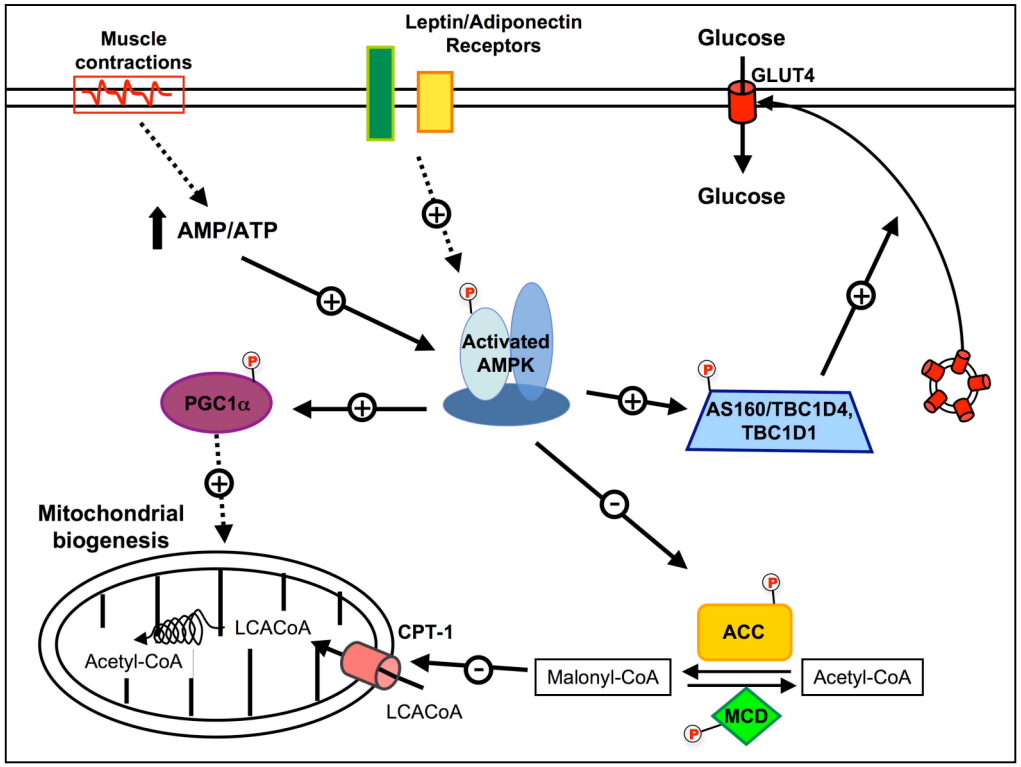

Figure 3. AMPK and the regulation of skeletal muscle metabolism. Proposed model for the role of AMPK in the regulation of lipid and glucose metabolism in skeletal muscle. AMPK activity may be increased by an altered energy nucleotide or by hormonal action. This activation of AMPK may result in an increase in glucose transport as well as an increase in fatty acid oxidation. ACC, acetyl-CoA carboxylase; AMPK, AMP-activated protein kinase; AS160, Akt substrate of 160kDa; CPT1-α, carnitine palmitoyl transferase-1; Glut4, glucose tranporter 4; MCD, malonyl-CoA decarboxylase; PGC1α, PPARγ co-activator 1α; LCACoA, Long Chain acyl CoAs.

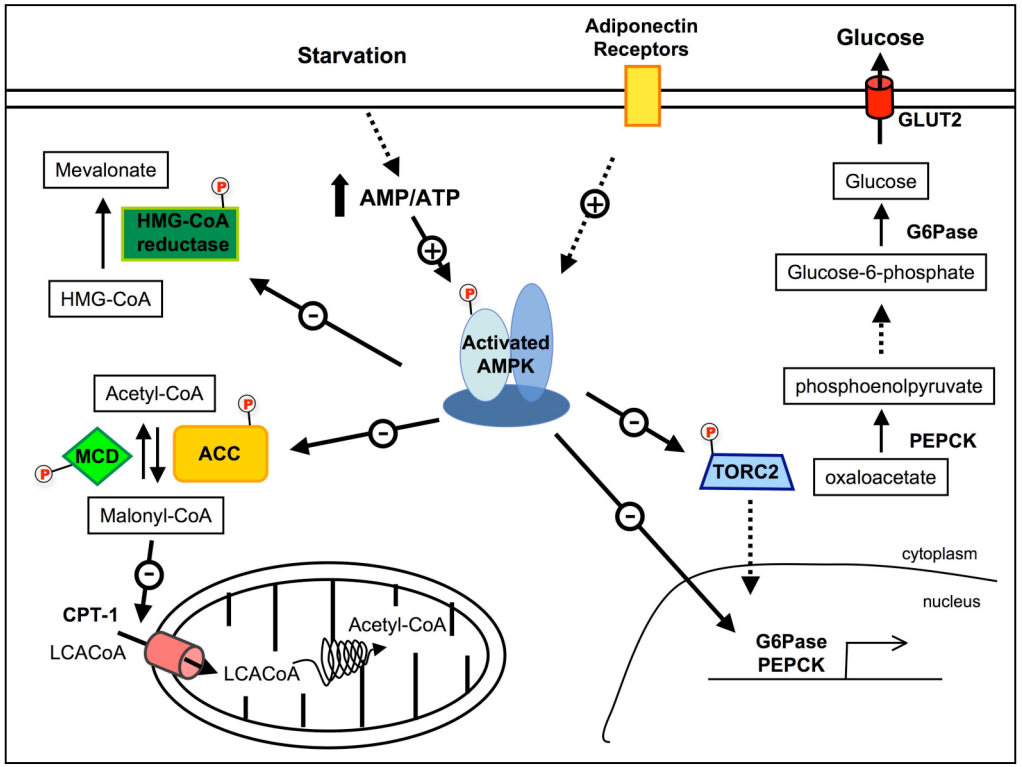

Figure 4. AMPK and the regulation of hepatic metabolism. Activation of AMPK leads to the inhibition of cholesterol synthesis by the phopshorylation of HMG-CoA reductase. By inhibiting ACC and activating MCD, AMPK increases fatty acid oxidation via the regulation of malonyl CoA levels, which is both a critical precursor for biosynthesis of fatty acids and a potent inhibitor of CPT-1, the shuttle that controls the transfer of LCACoA into the mitochondria. AMPK inhibits hepatic glucose production via the phosphorylation of TORC2 and inhibition gene expression for key gluconeogenic enzymes, G6Pase and PEPCK, and for the transcriptional co-activator PGC-1α. ACC, acetyl-CoA carboxylase; AMPK, AMP-activated protein kinase; CPT1-α, carnitine palmitoyl transferase-1; G6Pase, glucose-6-phosphatase; LCACoA, Long Chain acyl CoAs; MCD, malonyl-CoA decarboxylase; PEPCK, phosphoenolpyruvate carboxykinase; PGC1α, PPARγ co-activator 1α; TORC2, transducer of regulated CREB activity 2.