# Dynamic regulation of mitochondrial metabolism in metabolic disease

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**Rapid alterations in cellular metabolism allow tissues to maintain homeostasis during changes in energy availability. The central metabolic regulator acetyl-CoA carboxylase 2 (ACC2) is robustly phosphorylated during cellular energy stress by AMP-activated protein kinase (AMPK) to relieve its suppression of fat oxidation. While ACC2 can also be hydroxylated by prolyl hydroxylase 3 (PHD3), the physiological consequence thereof is poorly understood. We find that ACC2 phosphorylation and hydroxylation occur in an inverse fashion. ACC2 hydroxylation occurs in conditions of high energy and represses fatty acid oxidation. PHD3-null mice demonstrate loss of ACC2 hydroxylation in heart and skeletal muscle and display elevated fatty acid oxidation. Interestingly, PHD3 senses glucose and suppresses lipid metabolism, which is the most important dynamic regulation of fuel utilization in muscle in the exercise model. To understand the loss of PHD3 in skeletal muscle in physiology, we investigated muscle function with exercise capacity. Whole body or skeletal muscle-specific PHD3 loss enhances exercise capacity during an endurance exercise challenge. In sum, these data identify an unexpected link between AMPK and PHD3, and a role for PHD3 in acute exercise endurance capacity and skeletal muscle metabolism.**

**Keywords: Prolyl hydroxylase 3; acetyl-CoA carboxylase 2 modification; muscle physiology; exercise capacity; fat catabolism.**