Guest lecture

Function and Compartmentalization of Acyl-CoAs

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10.15 AM in BMB seminar room

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Abstract: Both heart and skeletal muscle modify their use of different fuels, depending on substrate availability and physiological requirements. Impaired capacity to switch between fatty acid (FA) and glucose oxidation is linked to disordered tissue and metabolic homeostasis. To understand how FA oxidation affects local and systemic glucose metabolism, we studied mice with heart-specific (*Acsl1*$^{H-/-}$) and skeletal muscle-specific (*Acsl1*$^{M-/-}$) deficiencies of long-chain acyl-CoA synthetase-1 (ACSL1). In both tissues, ACSL1 deficiency causes a 90% loss of total ACSL activity and 60-85% decreases in FA oxidation. *Acsl1*$^{H-/-}$ hearts show impaired mitochondrial respiratory function, increased mTORC1-related hypertrophy, blocked mitophagy, and abnormal cardiolipin composition. Compared to littermate controls, *Acsl1*$^{M-/-}$ mice are more insulin-sensitive, and during an overnight fast, their respiratory exchange ratio is higher, indicating greater glucose use. During endurance exercise, *Acsl1*$^{M-/-}$ mice run only 48% as far as controls. At the time that *Acsl1*$^{M-/-}$ mice are exhausted but control mice are continuing to run, liver and muscle glycogen and triacylglycerol stores are similar in both genotypes; however, *Acsl1*$^{M-/-}$ plasma glucose concentrations are ~40 mg/dl, whereas control glucose levels are ~90 mg/dl. Excess use of glucose and the likely use of amino acids for fuel within muscle depletes glucose reserves and diminishes substrate availability for hepatic gluconeogenesis. Surprisingly, the content of muscle acyl-CoA at exhaustion is markedly elevated, indicating that acyl-CoAs synthesized by other ACSL isoforms are not available for β-oxidation. These data suggest that the function of ACSL1 differs in different tissues and that compartmentalization of acyl-CoAs in muscle results in both an excessive glucose requirement and severely compromised systemic glucose homeostasis. We must now consider the mechanism by which acyl-CoAs are compartmentalized within cells.

Host: Professor Nils J. Færgeman, Department of Biochemistry and Molecular Biology, SDU.