SFB Guest Lecture Series

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Plasma lipid regulation of energy expenditure

Plasma lipids are established fuel sources and indicators of metabolic health, but their role as signals of inter-organ communication is just beginning to be appreciated. A major barrier in understanding lipid function is transport, because lipids are hydrophobic, they localized to lipoprotein complexes or extracellular vesicles in the blood. Despite the critical role of lipoproteins in lipid routing, little is known about how lipoprotein association alters lipid function. Using the selective pressure of cold exposure in mice, which rapidly shifts plasma lipid composition, we determined that very long chain ceramides are increased with cold exposure and localized to high density lipoprotein (HDL) particles. These plasma ceramides are synthesized in the liver and taken up by brown adipocytes. Inhibition of ceramide synthesis by myriocin treatment, ablates ceramide production and causes cold intolerance. HDL-associated ceramides are transferred from HDL particles to brown adipocytes through the ApoA1 receptor, SR-B1, where ceramides regulate B3-adrenergic receptor phosphorylation to then increase energy expenditure. These results demonstrate an inter-organ cellular lipid signaling pathway that is dependent on lipoprotein localization to regulate energy expenditure. Understanding lipoprotein localization and the impact on function will allow us to probe the causal relationship between ceramides and metabolic disease.