【Outstanding Academic Research Meeting 1-3】

Metabolites from Thermogenic Adipocytes as Signaling Molecules in Glucose and Energy Metabolism Regulation

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Thermogenic fats, including brown adipose tissue (BAT) and beige fat, utilize glucose and fatty acids as fuels to generate heat in response to cold, a process known as thermogenesis. Beyond their thermogenic function, these adipocytes act as endocrine organs, secreting metabolites, lipids, and proteins to communicate with other tissues and maintain systemic energy and glucose metabolism. As a result, obese individuals with high thermogenic activity exhibit improved blood glucose and triglyceride control and have a lower risk of developing type 2 diabetes and cardiovascular diseases. However, the mechanisms by which thermogenic adipocytes regulate glucose and energy metabolism remain unclear. To address this, we employed targeted liquid chromatography-tandem mass spectrometry to identify BAT-derived lipid mediators and their biological functions under cold stimulation. Our findings revealed that cold exposure enhances the biosynthesis and release of 12-lipoxygenase (12-LOX) metabolites from BAT. Among these, 12-hydroxyeicosapentaenoic acid (12-HEPE) acts on adipocytes and skeletal muscle to promote glucose uptake through an insulin-like signaling pathway. Additionally, cold stimulation induces BAT to secrete maresin 2 (MaR2), a specialized pro-resolving lipid mediator that targets liver macrophages to resolve obesity-induced inflammation. Notably, mice lacking 12-LOX in BAT failed to produce these lipid mediators, resulting in impaired glucose homeostasis and thermogenesis in cold environments. These findings underscore the critical role of BAT-derived lipid mediators in regulating whole-body glucose homeostasis and inflammation, highlighting their potential as therapeutic targets to combat obesity and metabolic disorders.