

内分泌代謝・糖尿病内 (島野 仁)

Endocrinology and Metabolism (SHIMANO Hitoshi)



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脂肪酸の量と質に視点においた脂質研究 ~生活習慣病やすべての生命現象、病態に向けた医療応用~

代謝は細胞、組織、個体いずれのレベルでも生命現象の根幹です。最近では、metaflammation, immunometabolism, cancer metabolism, brain metabolism といわれるように炎症、細胞増殖、免疫、がん、脳科学などの各領域で個別に注目されています。われわれもSREBP, CREBH, Elovl6など独自の脂質代謝研究から同様の展開を経験してきました。特に発見した脂肪酸伸長酵素のノックアウトマウスの研究から、脂質の量だけでなく質の視点：脂肪酸の組成（脂肪酸鎖長）がインスリン抵抗性や生活習慣病病態をはじめとしてあらゆる生命現象に影響することを見出し、脂肪酸鎖長を軸とした新しい医療戦略を提唱しています。この酵素を標的や脂肪酸の種類、組成に基づいた食事療法など新しい概念に関する特許申請、創薬にむけたプロジェクトを展開したいと考えています。もう一つの重要な標的はエネルギーセンサー分子です。CtBP2はハブメタボライトを検知して、細胞内及び臓器間の代謝制御を担います。ヒューマニクスでは、新しい領域と融合して分子構造やメカニズムを可視化して操作することが目標です。

Lipid research in the light of lipid quantity and quality ~ medical strategy towards biological events and pathologies~

Metabolism is one of the fundamental biological events at the level of cells, tissues, and body. Recently, more attention is being individually gained in the light of metaflammation, immunometabolism, cancer metabolism, and brain science. We have studied lipid metabolism, and through SREBP, CREBH, and Elovl6 similarly experienced our own extensions in different areas. Especially, Elovl6, identified as a novel long fatty acid elongase regulates fatty acid composition. Lessons from the KO mice implicate that this "lipid quality" regulates insulin resistance, life-related diseases, and furthermore, a wide variety of biological phenomenon, which tempts us to extend a novel medical strategy with elovl6, fatty acid chain length, and potentially food fatty acid composition as targets. Another target of concept is energy sensing system. Recent data suggest that energy sensor molecules including CtBP2 sense hub metabolite and regulate energy metabolism inside the cells and potentially connecting inter-organ metabolism. **In Humanics, we attempt to understand molecular structure and mechanism through fusion with new areas.**

1. SREBP-regulated lipid metabolism: convergent physiology-divergent pathophysiology. *Nat Rev Endocrinol.* 2017
2. Transcriptome network analysis identifies protective role of the LXR/SREBP-1c axis in murine pulmonary fibrosis. *JCI Insight.* 2019
3. Critical role of CREBH-mediated induction of TGF-β2 by HCV infection in fibrogenic responses in hepatic stellate cells. *Hepatology.* 2017
4. SREBP1 Contributes to Resolution of Pro-inflammatory TLR4 Signaling by Reprogramming Fatty Acid Metabolism. *Cell Metab.* 2017
5. KLF15 Enables Rapid Switching between Lipogenesis and Gluconeogenesis during Fasting. *Cell Rep.* 2016
6. Crucial role of a long-chain fatty acid elongase, Elovl6, in obesity-induced insulin resistance. *Nat Med* 2007

