第54回シグナル伝達医学　グローバルCOE学術講演会

“Small Molecule Inhibition of Phosphatidylcholine Transfer Protein/ StARD2 Ameliorates Diet-Induced Diabetes in the Mouse”

日時：2012年2月8日（水）18：00～
場所：外来診療棟5F　B講義室

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<Abstract>

Phosphatidylcholine transfer protein (PC-TP, synonym StARD2), a member of the steroidogenic acute regulatory protein–related transfer (START) domain superfamily, is a highly specific lipid binding protein with accentuated hepatic expression. Although it catalyzes the intermembrane exchange of phosphatidylcholines *in vitro*, PC-TP regulates glucose metabolism apparently upon sensing the fatty acid composition of membrane phospholipids. Coding region PC-TP polymorphisms confer protection against measures of insulin resistance: Human subjects exhibit a lower risk of harboring atherogenic small dense LDL particles, and New Zealand Obese mice are protected against developing polygenic type 2 diabetes. We provide a direct demonstration that *Pctp*$^{-/-}$ mice are resistant to diet-induced diabetes due to reduced hepatic glucose production. We identify an optimized small molecule inhibitor that bound PC-TP, displaced phosphatidylcholines from the lipid binding pocket and increased the thermal stability of the protein. Administration of the compound to wild type mice ameliorated glucose intolerance associated with high fat feeding, but had no activity in *Pctp*$^{-/-}$ mice. In cell culture systems, the small molecule inhibitor increased phosphorylation of key insulin signaling molecules in an insulin-independent manner, suggesting a mechanism of action that is distinct from commonly utilized insulin-sensitizing agents. These findings reveal PC-TP inhibition as a novel therapeutic strategy in the management of type 2 diabetes.

David E. Cohen教授は、脂質代謝学、肝臓病学の世界的権威であり、米国における著名なClinician-Scientistの先生です。これまでに、脂質結合タンパク「phosphatidylcholine transfer protein」の役割を中心に、さまざまな角度から、糖尿病や脂肪肝における脂質代謝研究を進められておられます。
たいへん、人柄もよい先生で、みなさまにわかりやすく講演していただく予定です。皆様の積極的な参加をお待ちしています。

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