ERATO末松ガスバイオロジープロジェクト
慶應義塾大学医学部医化学教室　共同講演会
グローバルCOEプログラム『In vivoヒト代謝システム生物学拠点』共催

◇10月13日（水）10時～

◇総合医科学研究棟　1階ラウンジ

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◆演題：Plasticity of Ito cells: Roles of Morphogens and Epigenetic Regulation

Ito cells (hepatic stellate cells) are vitamin A-storing liver sinusoidal pericytes that serve as a primary cell type to facilitate mesenchymal-epithelial interactions for a homeostatic control of liver parenchymal. Upon a wound healing or regenerative trigger, they reprogram cell fate regulation via expression of morphogens and undergo myofibroblastic trans-differentiation in a manner as to recapitulate the cell fate seen in embryonic liver development. However, in chronically injured adult livers, excessive scar ensues as a major consequence of this reprogramming. A decade ago, we identified the adipogenic gene *Pparγ* as a key differentiation gene suppressed in myofibroblastic trans-differentiation of Ito cells. Our recent research discloses activation of *Wnt*, *Necdin*, *Dlk1, and Shh* that culminate to epigenetic repression of *Pparγ*. This repression is mediated in part by a crosstalk between miR132 and miR137 resulting in enhanced expression and recruitment of the methyl CpG binding protein MeCP2 to the *Pparγ* promoter and increased H3K27 di- or tri-methylation at the *Pparγ* exons via EZH2 induction. We also identify the cAMP-CREB pathway as an upstream signaling for miR132 that is negatively regulated by NOX-mediated oxidant stress. Thus, our epigenetic mechanisms begin to link and explain the molecular basis of anti-fibrogenic cAMP-CREB pathway and pro-fibrogenic NOX pathway, and to provide potential therapeutic targets for cirrhosis.

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