論文の内容の要旨

論文題目　The study of novel PPARα agonist K-877 regulated genes in mouse liver and primary human hepatocytes.
（マウス肝臓およびヒト初代培養肝細胞において
新規PPARαアゴニストK-877によって制御される遺伝子に関する研究）

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To predict pharmacological and toxicological effects of a novel PPARα modulator (sPPARMα) K-877, comprehensive transcriptome analyses were performed in mouse liver and primary human hepatocytes. Gene expression profile of K-877 treated mouse liver clearly indicated that K-877 induces very long- and long-chain fatty acid β-oxidation related genes expression. Although almost all regulated genes by K-877 were also regulated by fenofibrate treatment, some K-877 regulated genes were not significantly regulated by fenofibrate suggesting K-877 has a function as sPPARMα. In addition, almost all genes regulated by K-877 treatment in wild type mouse are not affected by K-877 treatment in PPARα KO mouse. These results indicating that regulation of genes expression by K-877 is mainly mediated through PPARα activation. I also found that K-877 up-regulates several mitochondrial FA β-oxidation related genes expression in human hepatocytes as seen in mouse liver. By contrast, Pex1 and Pex3, peroxisomal biogenesis-related genes whose expression are apparently induced in K-877 treated mice liver, expression were not induced by K-877 treatment in human hepatocytes suggesting clinical dose of K-877 does not induce peroxisome proliferation and related untoward reaction in humans. In addition, K-877 induced the beneficial candidate genes (VLDLR, FGF21, ABCA1, MBL2, ENPEP) expression in primary human hepatocytes and these genes induction were stronger than those of fenofibric acid treatment.

Taken together, these results indicated that K-877 regulates hepatic gene expression as a sPPARMα and also suggested that K-877 may improve not only dyslipidemia, but also metabolic disorders such as metabolic syndrome and type 2 diabetes.