發育演化論文評介

謝豐舟教授

Forced expression of fibroblast growth factor 21 reverses the sustained impairment of liver regeneration in hPPARα^{PAC} mice due to dysregulated bile acid synthesis

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Abstract

Peroxisome proliferator activated receptor α (PPARα) stimulates hepatocellular proliferation is species-specific. Activation of mouse, but not human, PPARα induces hepatocellular proliferation, hepatomegaly, and liver cancer. Here we tested the hypothesis that human and mouse PPARα affects liver regeneration differentially. PPARα-humanized mice (hPPARα^{PAC}) were similar to wild type mice in responding to fasting-induced PPARα signaling. However, these mouse livers failed to regenerate in response to partial hepatectomy (PH). The liver-to-body weight ratios did not recover even 3 months after PH in hPPARα^{PAC}. The mouse PPARα-mediated down-regulation of *let-7c* was absent in hPPARα^{PAC}, which might partially be responsible for impaired proliferation. After PH, hPPARα^{PAC}displayed steatosis, necrosis, and inflammation mainly in periportal zone 1, which suggested bile-induced toxicity. Quantification of hepatic bile acids (BA) revealed BA overload with increased hydrophobic BA in hPPARα^{PAC}. Forced FGF21 expression in partial hepatectomized hPPARα^{PAC} reduced hepatic steatosis, prevented focal necrosis, and restored liver mass. Compared to mouse PPARα, human PPARα has a reduced capacity to regulate metabolic pathways required for liver regeneration. In addition, FGF21 can compensate for the reduced ability of human PPARα in stimulating liver regeneration, which suggests the potential application of FGF21 in promoting hepatic growth in injured and steatotic livers in humans.

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研究人員發現：小鼠與人類的肝臟再生有不同之處，主要的差異是和一種**PPARa**蛋白質有關。
小鼠的**PPARa**比人類活躍而且有效，所以白鼠肝臟的再生比人類快速。研究人員發現**FGF 21**能夠增進人類**PPARa**的肝臟再生功能。因此，**FGF21**對人類肝臟移植和肝病可能具有治療的潛力。

在手術切除三分之二肝臟之後，白鼠在七至十天，肝臟會長回原來的大小。帶有人類**PPARa**的小鼠，肝臟再生的能力就較差，不過使用**FGF21**就可以提升其肝臟再生功能。

白鼠的**PPARa**雖然具有較強的肝臟再生作用，但卻會導致肝臟癌症。人類**PPARa**的肝臟再生能力雖然較弱，但卻不會引發癌症。

目前已有幾種以**PPARa**為標的之藥物，用來治療高膽固醇及高血脂。因此，將來在某些適當的情況，例如，肝臟移植，病毒或酒精引起的肝臟損傷，使用**FGF21** 來提升人類**PPARa**的肝臟再生功能，可能具有臨床用途。