学 位 論 文 の 要 旨

氏名　　山本　佳生

学 位 論 文 名　Role of Peroxisome Proliferator-activated Receptor γ During Liver Regeneration in Rats
発 表 雑 誌 名　Journal of Gastroenterology and Hepatology
（巻，初頁～終頁，年）　In press

著 者 名　Yoshio Yamamoto, Takashi Ono, Dipok Kumar Dhar, Akira Yamanoi, Mitsuo Tachibana, Tsuneo Tanaka, and Naofumi Nagasue

論 文 内 容 の 要 旨

INTRODUCTION

Peroxisome proliferator-activated receptor γ (PPARγ), a member of the nuclear receptor superfamily, is widely expressed in adipocytes and other tissues including the liver. It has been demonstrated that 15-deoxy-Δ12,14-prostaglandin J2 (15d-PGJ2), a metabolite of prostaglandin D2, serves as a potential endogenous ligand for the PPARγ. Whereas thiazolidinediones such as pioglitazone are specific exogenous agonistic ligands for PPARγ Several reports have shown that PPARγ activation induced cell cycle arrest and apoptosis in tumor cells. We investigated expression of PPARγ and serum level of 15d-PGJ2 in rats after 70% partial hepatectomy (PH). Furthermore, the effect of oral administration of pioglitazone on liver regeneration following PH in rats was evaluated in terms of PPARγ/ligand system, cell cycle, and liver volume recovery.

MATERIALS AND METHODS

Expression of PPARγ and serum level of 15d-PGJ2 by enzyme immunoassay was evaluated in rats following partial hepatectomy (PH group). Furthermore, the effect of PPARγ agonist, pioglitazone, on liver regeneration (PH + PGZ group) was evaluated by proliferating cell nuclear antigen labeling index, relative liver weight, and expression of cell cycle regulators.

RESULTS AND DISCUSSION

The number of PPARγ stained hepatocytes decreased at 24 h (PH, 15.8 ± 2.2%; sham, 35.5 ± 2.4%; $p < 0.001$) and increased in the late phase of liver regeneration compared to sham operated group ($p < 0.001$ at 48 - 120 h). The peaks of serum 15d-PGJ2 (627.0 ± 91.1 pg/ml) and PPARγ expression (90.6 ± 3.1%) coincided in the late phase of liver regeneration. Our results suggest that PPARγ stimulation by 15d-PGJ2 might be one of growth inhibitory signals in hepatocyte proliferation after PH.

Also oral administration of pioglitazone inhibited hepatocyte proliferation, in terms of PCNA labeling index and p27 expression, during the late phase of liver regeneration and caused a transient reduction in liver mass when compared to PH group. In this study, the PCNA labeling index was slightly lower in the PH + PGZ group at 24 h after PH and significantly lower at 48 - 72 h when compared to the PH group. These results suggest that the differences of PCNA labeling index and also liver volume recovery during the late phase of liver regeneration is probably attributable to the activation of PPARγ/ligand system by pioglitazone, and that the change of PPARγ activation by pioglitazone might lead to the inhibition of liver regeneration after PH. In terms of the effect of pioglitazone, several reports have shown that agonistic ligands for PPARγ inhibited proliferation by arresting growth at G1-S phase of cell cycle. Our results showed that, treatment with pioglitazone induced inhibition of hepatocyte proliferation is not mediated through an inhibition of cell cycle proteins such as cyclin D1 and cyclin E rather that it was executed by an augmentation of expression cell cycle inhibitory protein p27. The exact

mechanism of cell cycle withdrawal induced by PPARγ agonists is not yet clear but these results suggest that the oral administration of pioglitazone might affect cell growth regulation during the late phase of liver regeneration.

CONCLUSION

These results indicate that PPARγ/ligand system may be one of the key negative regulators of hepatocyte proliferation and may be responsible for the inhibition of liver growth in the late phase of liver regeneration.