Tumor protein p53-induced nuclear protein 1 (TP53INP1) in spontaneous chronic pancreatitis in the WBN/Kob rat: drug effects on its expression in the pancreas

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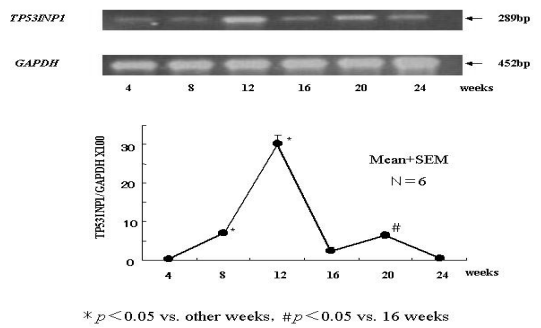
TP53INP1 is a nuclear factor that is rapidly and strongly induced by various stresses. TP53INP1 is overexpressed in acinar cells during acute pancreatitis in the mouse. TP53INP1 overexpression promotes cellular apoptosis. It is known acinar cell apoptosis is involved in acinar destruction/degeneration in the course of chronic pancreatitis. Therefore, examining TP53INP1 gene expression in CP and related to acinar cell apoptosis will contribute to a better understanding of the molecular mechanisms of the onset and progression of chronic pancreatitis.

Four-week-old male WBN/Kob rats were fed a special breeding diet MB-3 to induce chronic pancreatitis. Anti-inflammatory drug such as camostat mesilate (0.01%) and Saiko-keishi-to (0.08%) were mixed in the diet MB-3 fed to the rats from 4 weeks. Sections were stained with hematoxylin and eosin for histological evaluation. TP53INP1 mRNA expression was determined by RT-PCR with a semi-quantitative analysis and *in situ* hybridization. TUNEL was used to detect cell apoptosis. *In vitro*, 5 mg /ml L-arginine was dissolved in the medium of AR4-2J cell.

TP53INP1 mRNA expression began at 4 weeks, reached its first peak at 12 weeks, after decreased at 16 weeks, TP53INP1 mRNA reached its second peak at 20 weeks, finally decreased at 24 weeks. By *in situ* hybridization analysis, TP53INP1 mRNA was strong in the acinar cells but absent in duct or islet cells. The apoptotic index was significantly increased at 12 and 20 weeks showing two peaks, so that, the kinetics of TP53INP1 mRNA expression was paralleled to apoptotic index. TP53INP1 mRNA expression was significantly suppressed in the camostat mesilate group at 8, 12, and 20 weeks, and it was also significantly suppressed in the Saiko-keishi-to treated group at 8 and 12 weeks. TP53INP1 mRNA was expressed in AR4-2J cells from 2 to 24 hours. The expression level was significantly higher at 6 hr than those at other time points.

In the present study, TP53INP1 expression showed two peaks in the course of WBN/Kob rat. The first peak of TP53INP1 would reflect the concomitant induction of pro-, and anti-apoptotic factors at the onset of chronic pancreatitis. Around this time point, the histopathology of the pancreas resembles acute edematous pancreatitis, although there is already pancreatic fibrosis. Acinar cell apoptosis would attenuate the severity of pancreatitis, preventing the excessive release of harmful pancreatic enzymes. The second peak of acinar cell apoptosis and pro-apoptotic factors including TP53INP1 could reflect acinar cell loss and acinar remodeling or regeneration during the progression of chronic pancreatitis. Suppression of TP53INP1 mRNA expression by therapeutic drugs may confirm that TP53INP1 expression is deeply involved in the onset and progression of chronic pancreatitis in this model.

In conclusion, we have shown that TP53INP1 mRNA expression is induced in the onset and progression of chronic pancreatitis in WBN/Kob rats. TP53INP1 may be involved in the pathogenesis of chronic pancreatitis as a pro-apoptotic factor.



*$p<0.05$ vs. other weeks, #$p<0.05$ vs. 16 weeks

Figure: TP53INP1 mRNA was expressed from 4 to 24 weeks. It showed the first peak at 12 weeks and the second peak at 20 weeks.