LIVER

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# The effect of a tumour necrosis factor antibody on the regenerative response after partial hepatectomy in rats

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Abstract In this study we investigated the effect of tumour necrosis factor (TNF) on the regenerative response after partial hepatectomy. Adult male rats were injected intravenously with an antibody to TNF immediately after partial hepatectomy. Animals were sacrificed at 0, 24, 48, 72 and 96 h postoperatively. Hepatic thymidine kinase (TK) activity, liver weight to body weight (LW/BW) ratio, and mitotic index (MI) were used as indices of hepatic regeneration. The rats treated with TNF-Ab had significantly lower levels of TK

activity in the liver at 24 h postoperatively compared to the saline treated animals. Furthermore the peak hepatic TK activity was delayed to 48 h in the rats treated with TNF-Ab. The mitotic indices and LW/BW ratios in the TNF-Ab- and saline-treated animals were similar. These data suggest that TNF potentiates the regenerative response after partial hepatectomy.

Key words Tumour necrosis factor · Partial hepatectomy

## Introduction

## Methods

Several cytokines have been shown to modify the regenerative response after partial hepatectomy [1]. Tumour necrosis factor (TNF) is produced primarily by activated monocytes/macrophages and appears to potentiate hepatic regeneration. Most previous studies have utilized exogenously administered TNF [2, 3]. In the present study an anti-TNF antibody was used to neutralize endogenous TNF after partial hepatectomy in rats. Conventional parameters of hepatic regeneration were used to compare the regenerative response in anti-TNF antibody treated animals with the control saline-treated rats after partial hepatectomy. Adult male Long Evans rats weighing 250 to 300 g were subjected to either 70% partial hepatectomy (PH) or sham operation (SH) and randomly allocated to the following treatment groups:

Group 1: PH + N/Saline Group 2: PH + 2 mg anti-TNF-antibody Group 3: PH + 6 mg anti-TNF-antibody Group 4: SH + 6 mg anti-TNF-antibody

The anti-TNF-antibody and the N/Saline were injected intravenously immediately postoperatively.

Groups of animals were sacrified at 0, 24, 48, 72 and 96 h postoperatively. The rats were sacrified by exsanguination and the resected livers were used to determine the liver weight to body weight (LW/BW) ratio, the hepatic thymidine kinase (TK) activity and the mitotic index. The hepatic TK activity was determined by measuring the in vitro conversion of thymidine to thymidine phosphate [4].

#### Methods

There was a significant increase in TK activity at 24 h after partial hepatectomy (Table 1). Animals treated with TNF-Ab after partial hepatectomy had lower levels of TK activity at 24 h postoperatively compared to the saline treated animals; furthermore the peak in the TK activity was delayed to 48 h postoperatively.

The liver weight to body weight ratios at 24 h postoperatively were consistent with a 70% partial hepatectomy and increased thereafter to almost reach preoperative values by 96 h (Table 2). The LW/BW ratio was not modified by the injection of TNF-Ab postoperatively.

There was a significant increase in the mitotic indices at 48 h postoperatively (Table 3). Mitotic indices in the TNF-Ab-treated and saline-treated animals were similar.

### Discussion

Endotoxin is responsible for an enhanced regenerative response after PH and this effect is thought to be mediated via TNF [5]. Exogenously administered TNF causes an increase in hepatic DNA synthesis in intact livers as well as after partial hepatectomy [2, 3]. In this study rats treated with a TNF-Ab after partial hepatectomy had lower levels of and a delay in the peak of the thymidine kinase activity. These results further implicate TNF in the control of hepatic regeneration and extend previous findings which showed that treatment with antibodies to TNF inhibited the regenerative response after partial hepatectomy [6]. In this study hepatic regeneration was both suppressed and delayed.  
 Table 1
 Hepatic TK activity in rats treated with either saline or TNF-Ab after partial hepatectomy or sham operation

	TK activity (dpm/mg protein $\times$ 103)			
	Non-operated controls	24 h	48 h	
PH + N/Saline	2.8+0.3	54 + 7	33+11	
PH + 2 mg TNF-Ab	$2.8 \pm 0.3$	36 + 15	45+11	
PH + 6 mg TNF-Ab	$2.8 \pm 0.3$	16+ 3	47 + 9	
SH + 6 mg TNF-Ab	2.8+0.3	1.9+0.3	1.6+0.4	

 Table 2
 LW/BW ratio in rats treated with either saline or TNF-Ab after either partial hepatectomy or sham operation

	LW/BW ratio ( $\times 10^{-3}$ )		
	Non-operated controls	24 h	48 h
PH + N/Saline	412	165 + 7	238+17
PH + 2 mg TNF-Ab	412	169 + 24	232 + 15
PH + 6 mg TNF-Ab	412	156 + 11	203 + 16
SH + 6 mg TNF-Ab	412	400 + 26	365 + 3

 Table 3
 Mitotic indices in rats treated eith either saline of TNF-Ab

 after either partial hepatectomy or sham operation

	Mitotic index		
	Non-operated controls	24 h	48 h
PH + N/Saline	0	0.8	24
PH + 2 mg TNF-Ab	0	0.4	26
PH + 6 mg TNF-Ab	0	0.6	31
SH + 6 mg TNF-Ab	0	0	0

In summary, the present data supports previous studies which suggest that TNF potentiated hepatic regeneration after PH. The precise mechanism by which TNF modulated the regenerative response after PH remains unresolved.

## References

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