

## GENETIC OR PHARMACOLOGICAL INHIBITION OF TNF- $\alpha$ REDUCED SPLANCHNIC ISCHEMIA AND REPERFUSION INJURY

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In the present study, we used tumour necrosis factor-R1 knock out mice (TNF- $\alpha$ R1KO) to evaluate a possible role of TNF- $\alpha$  on the pathogenesis of ischemia and reperfusion injury of the multivisceral organs. Ischemia and reperfusion injury was induced in mice by clamping both the superior mesenteric artery and the celiac artery for 30 min, followed thereafter by reperfusion. Sixty minutes after reperfusion, animals were sacrificed for histological examination and biochemical studies. Injured wild-type(WT) mice developed a significant increase of ileum TNF- $\alpha$  levels, myeloperoxidase activity and marked histological injury and apoptosis. Ischemia and reperfusion injury of the multivisceral organs was also associated with a significant mortality. Reperfused ileum sections from injured-WT mice showed positive staining for P-selectin, V-CAM, ICAM-1 and E-selectin. The intensity and degree of P-selectin, E-selectin, VCAM and ICAM-1 were markedly reduced in tissue section from injured-TNF- $\alpha$ R1KO mice. Ischemia and reperfusion injured TNF- $\alpha$ R1KO mice showed also a significant reduction of neutrophils infiltration into the intestine, a reduction of apoptosis, an improved histological status of the intestine and survival. In addition, we also investigated the effect of Etanercept, a TNF- $\alpha$  soluble receptor construct, on ischemia and reperfusion injury of the multivisceral organs. Etanercept (5 mg/kg administered i.p. 5 min prior reperfusion) significantly reduced the inflammatory response and the ileum injury. Taken together, our results clearly demonstrate that TNF- $\alpha$  play an important role in the ischemia and reperfusion injury and put forward the hypothesis that modulation of TNF- $\alpha$  expression may represent a novel and possible strategy.