# PRODUCTION OF INTERLEUKIN-6 BY RAT HEPATOCYTES AND ITS REGULATION

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Acute phase proteins are synthesized by the liver in the acute phase of inflammation caused by infection or tissue injury. Interleukin (IL)-6 is one of the major mediators that induce the synthesis of acute phase proteins. It is well known that administration of a bacterial endotoxin (lipopolysaccharide ; LPS) produces a marked increase in the plasma concentration of IL-6. Although previous reports have shown that IL-6 is synthesized in various organs such as the spleen, liver and lung, the major source of the LPS-induced plasma IL-6 is still unclear. In this study, using rats as an experimental animal, I examined IL-6 synthesis in response to LPS and various cytokines *in vivo* and *in vitro*, with special reference to IL-6 synthesis in the liver.

When rats were given LPS (1 mg/kg of body weight) intraperitoneally, the tissue level of IL-6 mRNA was markedly increased in spleen and liver. The IL-6 mRNA level in liver was 25% of that in spleen when expressed as per g tissue, but it was about 5 times higher than that in the spleen, when estimated per organ, suggesting that the liver is one of major organs contributing to the increased plasma IL-6 in endotoxemia. To identify the cells producing IL-6 in the liver, *in situ* hybridization studies were performed using specific riboprobes for rat IL-6 mRNA. Clear signals for IL-6 mRNA were detected in hepatocytes as well as non-parenchymal cells.

To further confirm this, I isolated hepatocytes and non-parenchymal cells by collagenase digestion of liver, cultured them, and measured IL-6 released into the culture medium. IL-6 release from the non-parenchymal cells was increased by addition of LPS, but release of IL-1 or tumor necrosis factor (TNF) was not. In contrast, IL-6 released from hepatocytes was increased by IL-1 and also by IL-6 itself, but not by LPS and TNF.

These results suggest that IL-6 is synthesized in hepatocytes in response to IL-1 and IL-6 released from non-parenchymal cells after LPS stimulation. Hepatocyte-derived IL-6 may play a significant role in hepatic acute phase protein synthesis.