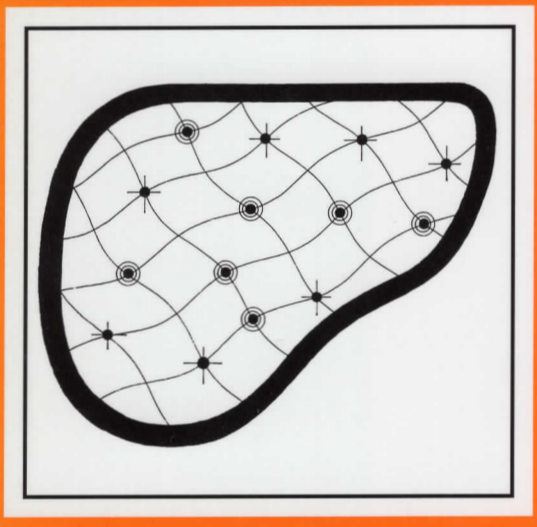
FALK SYMPOSIUM 125

Cytokines in Liver Injury and Repair



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Cytokines in Liver Injury and Repair

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19
Regulation of interleukin-6-type cytokine signalling

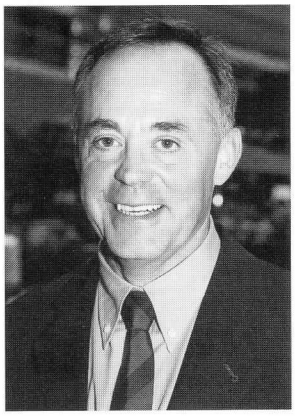
P. C. HEINRICH, A. BARTHEL, I. BEHRMANN, F. FELD, J. GRÖTZINGER, C. HAAN, H. M. HERMANNS, H.-G. JOOST, I. M. KERR, M. KORTYLEWSKI, U. LEHMANN, G. MÜLLER-NEWEN, S. RADTKE, R. ROTH, F. SCHAPER and A. TIMMERMANN

INTRODUCTION

The liver plays a pivotal role in the acute-phase response of the organism. It contains the largest pool of macrophages (Kupffer cells) of the body. On the other hand, hepatocytes are the major sites of acute-phase protein (APP) synthesis. Interleukin-6 (IL-6) has been identified as the major stimulator of APP synthesis in parenchymal cells of the liver. It belongs to a family of cytokines characterized by a 4-α-helix bundle topology. Besides IL-6, the cytokines IL-11, leukaemia inhibitory factor (LIF), ciliary neurotrophic factor, cardiotrophin-1, oncostatin M (OSM) and the recently discovered cardiotrophin-like cytokine are members of this family[1].

IL-6 exerts its action on hepatocytes via a surface receptor complex consisting of the α-receptor subunit gp80 and two signal transducing subunits (gp130). The binding of IL-6 to its α-receptor gp80 as well as the interaction of the IL-6/gp80 complex with the signal transducer gp130 has been studied in great detail[1]. The major steps in IL-6 signal transduction have been worked out independently in two laboratories[2,3]. The first event in IL-6 signalling is the binding of the ligand to its α-receptor, followed by the homodimerization of the signal transducer gp130 and the formation of a ternary complex. The IL-6-induced dimerization of gp130 initiates a phosphorylation cascade. The first step in this cascade is the transphosphorylation of tyrosine kinases of the Janus family (Jaks). The Janus kinases Jak1, Jak2, and Tyk2 – all constitutively bound to the membrane-proximal part of the cytoplasmic tail of gp130 – become tyrosine-phosphorylated and thus enzymatically active. Subsequently, tyrosine residues in the cytoplasmic part of gp130 are phosphorylated. These phosphotyrosines function as docking sites for

Scientific Organization:



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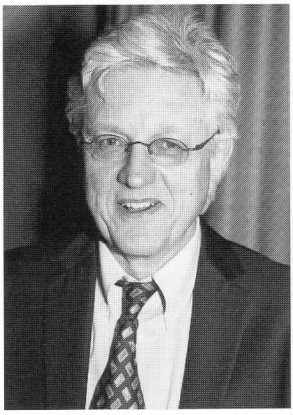

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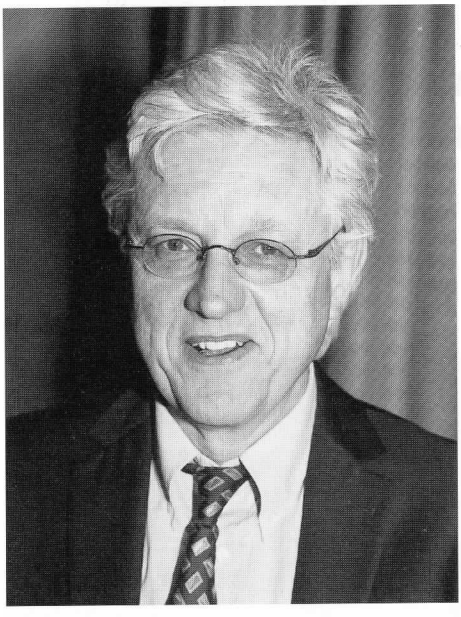
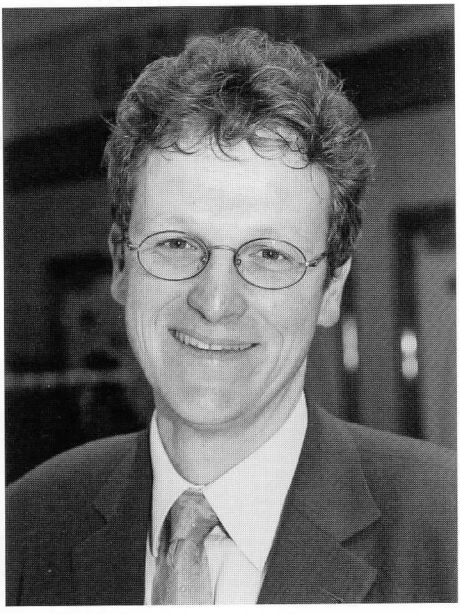


P. C. Heinrich



C. Trautwein

P. C. Heinrich (Aachen) discussed the **modulation and termination of IL-6-type cytokine signalling**. IL-6-type cytokines including IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor, and cardiotrophin signal through the activation of Janus kinases (Jaks) and the STAT (signal transducers and activators of transcription) factors. The Jak/STAT pathway involves receptor dimerization (gp130, LIFR, OSMR), tyrosine phosphorylation, recruitment of STAT factors and the tyrosine phosphatase SHP-2, translocation of tyrosine- and serine-phosphorylated STAT-dimers to the nucleus and binding of activated STATs to enhancer sequences of respective target genes resulting in transcriptional activation. P. C. Heinrich and coworkers have identified an epitope in Jak1 crucial for interaction with gp130 and demonstrated that association of Jak1 with the membrane proximal region of the receptor enhances its surface expression. Deletion of the OSMR-box1/2 region resulted in an increased surface expression indicating that this region may contain a signal preventing efficient receptor surface expression in the absence of associated Jak1. In his presentation P. C. Heinrich emphasized the mechanisms of termination and modulation of IL-6-type cytokine signalling, i.e. the role of the tyrosine phosphatase SHP-2, the role of SOCS feedback inhibitors, the importance of different half-lives of the signalling molecules gp130, Jaks, SHP-2, STATs and SOCS, the internalization of the receptor complexes and the cross-talk between the signalling pathways induced by IL-6 and IL-1β.

C. Trautwein (Hannover) lectured on **gp130-dependent pathways and their relevance in the liver**. IL-6 controls the acute phase response in hepatocytes and contributes to different physiological functions. In the presented study conditional knockout mice using the cre/loxP system were generated in which the exon 16 encoding the transmembrane domain of the gp130 receptor was flanked with loxP sites. These transgenic mice were cross-bred with animals controlling the Cre-recombinase under transcriptional control of the albumin promoter