

## **Summary**

Childhood precursor T cell ALL were investigated in vitro with respect to apoptosis in consideration of cell biological and clinical aspects. The following results were obtained:

### **1. Sensitivity to apoptosis-induction and expression of apoptosis-relevant regulation factors in precursor T cell ALL**

Cortical precursor T cell ALL represent the most sensitive subtype to drug-induced apoptosis.

The CD95-receptor/ligand-system is not essential for the induction of spontaneous apoptosis or drug-induced apoptosis in precursor T cell ALL.

Sensitivity to spontaneous and drug-induced apoptosis does not correlate with constitutive expression levels of Bcl-2 or Bax.

Spontaneous apoptosis can be explained by an upregulation of Bax in precursor T cell ALL.

Bax is involved in apoptosis-induction on the level of intracellular changes of localization from the cytosol to mitochondria.

### **2. IL-7 represents an antiapoptotic survival factor in precursor T cell ALL**

IL-7 represents an antiapoptotic survival factor in precursor T cell ALL which inhibits both, spontaneous apoptosis and apoptosis induced by the drugs dexamethasone and doxorubicin.

Cortical precursor T cell ALL represent the most sensitive subtype of ALL towards apoptosis-inhibition by IL-7.

Bcl-2 expression is upregulated during IL-7-induced inhibition of spontaneous apoptosis as well as during IL-7-induced inhibition of dexamethasone-induced apoptosis. Bcl-2

could function as a common regulatory factor in the IL-7- and dexamethasone-induced signaling pathway.

### **3. *In vitro* sensitivity to chemotherapeutic drugs and IL-7 – prognostic relevance for the response *in vivo***

*In vitro* sensitivity to dexamethasone correlates with early *in vivo* response to chemotherapy.

*In vitro* sensitivity to IL-7 correlates with early *in vivo* reduction of blasts and represents an independent parameter for the identification of precursor T cell ALL subtypes with differential sensitivity to apoptosis-induction.

Functional *in vitro* investigations of apoptosis provide valuable informations about cell biological characteristics of primary precursor T cell ALL cells. In combination with clinical data, these investigations could contribute to the understanding of the pathophysiology of precursor T cell ALL. Especially the sensitivity to glucocorticosteroids and cytokine-mediated modulation of apoptosis *in vitro* turned out to be a predictive factor for the response to induction therapy *in vivo*. In future studies, cell biological differences regarding the induction of programmed cell death offer the chance to develop specific therapeutic substances which, by selective induction of apoptosis, could contribute to an improvement of the response to therapy in precursor T cell ALL subtypes.