7 SUMMARY

The epidermal growth factor receptor (EGFR) is a promising target for innovative cancer therapy. EGFR-overexpression and/or dysregulation is described for several tumor entities and has been demonstrated to be important for tumor growth and progression.

Recently two classes of EGFR inhibitors have been developed: Tyrosine kinase inhibitors that target the catalytic domain of the EGFR such as gefitinib (Iressa^{TM}) and erlotinib (Tarceva^{TM}) and monoclonal antibodies like cetuximab (Erbitux^{TM}) that target the ligand-binding extracellular domain of the receptor.

The aim of this study was to investigate EGFR inhibition in hepatocellular (HCC) and esophageal carcinoma cell models. Experiments were performed using two established hepatocellular and three esophageal cancer cell lines, as well as primary cell cultures of human esophageal carcinoma.

Expression of the EGFR was demonstrated for all cell lines. EGFR-blockade by gefitinib, erlotinib or cetuximab significantly inhibited tumor cell growth. The antiproliferative effects observed were due to an induction of cell cycle arrest at the G_1-to-S transition as well as by induction of mitochondria-dependent apoptosis.

The underlying molecular mechanisms were elucidated. EGFR-blockade led to an inhibition of ERK1/2 as well as STAT activation which resulted in transcriptional changes of apoptosis and cell cycle regulating genes. Antiapoptotic members of the Bcl-2 family were found to be suppressed whereas proapoptotic caspases were overexpressed. The cell cycle inhibitors $p21^{Waf1/CIP1}$ und $p27^{Kip1}$ were overexpressed, while on the other hand the cell cycle promoter cyclin D1 was suppressed in response to EGFR inhibition. Additionally, growth arrest and DNA-damage inducible genes (gadds) being associated with apoptosis induction and cell cycle arrest were also found to be upregulated.

Furthermore, the expression of the insulin-like growth factor receptor 1 (IGF-1R), the transactivation of EGFR-mediated mitogenic signaling by IGF-1R and the inhibitory effects of EGFR-tyrosine kinase inhibition on the receptor-receptor cross talk were examined. On the basis of these findings, a novel approach to overcome resistance towards anti-EGFR based therapy strategies was established, for IFG-1R downstream signaling is known to be able to compensate for a blocked primary EGFR pathway.

Investigations on downstream EGFR signaling provided a rationale for future clinical investigations of anti-EGFR based combination therapy. The antineoplastic potency of conventional cytostatics was enhanced when EGFR was simultaneously inhibited. Moreover,

an isochronal inhibition of EGFR and IGF-1R as well as dual-agent blockade of the EGFR led to enhanced antineoplastic effects as compared to monotherapeutic approaches.

As similar results were obtained in HCC and esophageal carcinoma cells EGFR inhibition for cancer treatment appears to be a general principle and this work can be regarded as a proof of principle.

In conclusion, EGFR-inhibition represents a promising approach for the treatment of both HCC and esophageal cancer thus improving the limited treatment options for both tumor entities. The transfer of this innovative therapeutic concept should be evaluated *in vivo* and in clinical studies in the future.