6 summary

Development and Characterization of Human Tumor Models by Orthotopic Implantation

In this study the following human tumor xenografts were implanted orthotopically in nude mice: colon carcinoma CXF 1103T, bladder carcinoma BXF 1299T, prostate carcinomas PRXF PC3T, PC3MT, PC3MMT and the ascites model PRXF PC3MAS. In case of four models implanted tumor material derived from xenografts growing subcutaneously in nude mice. For implantation of PRXF PC3MT and PRXF PC3MAS orthotopically growing xenografts were used as donor material.

With the exception of PRXF PC3(T), take rates of orthotopic and ectopic models were similar. However, xenografts implanted into the orthotopic site grew faster than the xenografts at the heterotopic site.

These results confirm with the examinations of other groups. Low take rate of PRXF PC3T could not be explained by going through literature.

The fact that human tumor cells only metastasize when implanted in the corresponding organ was beared out in the present study. Median metastasis rate amounted to 74 %. Distribution of secondary lesions was almost similar to the situation in the corresponding patient. Correspondance as well as divergence from the patient tumor has been described but not explained before. Data presented in this study allow to suppose a correlation between the metastastic behavior of the tumor in the mouse and the different influences on the resected patient specimen before implantation.

Histologically, primary tumor and metastatic lesions were similar when human tumors were implanted in the corresponding organ of the nude mouse. The histology was not influenced by the transplantation site. Even the specimen obtained from the patient had histologically high similarities with the xenograft growing in nude mice. Thus, histological structure was not influenced by the tumor environment or host biology.

The expression of human cytokeratin was determined by immunohistochemistry. Since the expression was independent of localization of the tumor, measurement of cytokeratin was a feasible method to detect micrometastases. For colon carcinoma CXF 1103T the expression of carcinoembryogenic antigen (CEA) was determined. This xenograft did express the tumor marker irrespective of the implantation site. In patient serum however CEA-levels were not detectable. Originally, CXF 1103T was probably a low secreter, which means a tumor expressing CEA but not secreting it.

The results of histological and immunohistological examinations correlated well with the results of other groups.

Cytological examination of the ascites model showed no relation between tumor cell concentration or relative tumor cell number found in the pleural and peritoneal cavity on one hand and the number of injected tumor cells or their origin on the other hand.

The influence of the implantation site on structural quality of tumor vessels was discussed contrarily. Vascular permeability was not influenced by the implantation site. Apart from visceral metastases, these tumors retained much more dye than the primary tumors. Thus, the selective process of metastasis enhanced porosity of the tumor vessels.

For BXF 1299T and PRXF PC3MT chemosensitivity against standard anticancer agents was tested. Orthotopic implanted tumors turned out to be a feasible model for anticancer drug testing *in vivo*. In contrast to observations of other authors, chemosensitivity was not influenced by the localization of the tumor. The orthotopic models showed a slightly enhanced responsivness in comparison to their subcutaneous counterpart. This phenomenon could be explained by the fact that the chemosensitivity profile of the selected xenografts showed even in the subcutaneous model high correspondence with the patient tumor.

Thus, testing anticancer drugs in the subcutaneous model before turning to the large-scale orthotopic model seamed to be a appropriate strategy.

So far as the tested anticancer drugs showed antitumoral activity they also inhibited the development of metastases. Therefore, the examinated orthotopic models turned out to be suitable for development of antimetastatic drugs.

This study illuminated the importance of human orthotopic models in oncology. Developing antimetastastic drugs as well as testing of local therapies seem to be the most important application for the models described in this thesis. In addition, they allow to study different aspects of tumor biology and will facilitate the development of new anticancer strategies.