Abstract

Malignant gliomas belong to a highly aggressive class of tumours. Average patient survival time generally does not exceed 15 months. Despite intensive research, no therapeutic strategies capable of significantly extending the lives of those affected by the disease have been established to date.

One potentially viable area of research into possible therapeutic targets in cancer therapy focuses on cell surface proteases. This group of proteins includes dipeptidyl peptidase IV (DPP-IV). Changes to DPP-IV expression have been established in the case of various cancer types including malignant gliomas. Understanding the role of DPP-IV in the biological processes of this malignant disease may thus contribute to the development of new therapeutic modalities.

This thesis is therefore dedicated to establishing an orthotopic xenograft model as well as a genetically engineered model (GEM) of the glioma. The effects of DPP-IV on the growth of an experimental glioma were subsequently examined, as was the ratio of catalytic and non-catalytic mechanisms in this process. The GEM model was used for monitoring enzymatic activity and DPP-IV distribution. Non-invasive fluorescence imaging was employed in order to monitor the intraexperimental dynamics of experimental gliomas.

The results indicated that DPP-IV negatively influences glioma growth in the orthotopic xenograft model. This influence was found to be independent of its catalytic function. While the transgenic glioma model produced evidence of increased DPP-IV-like activity in comparison with control tissue, the growth of canonical DPP-IV was not statistically significant. The transgenic model indicated that while no changes took place in healthy brain tissue, changes in DPP-IV distribution occurred in model tumours. While DPP-IV was expressed in blood vessels and capillaries in healthy tissue, it was not expressed in newly formed dysplastic tumour capillaries. DPP-IV was expressed in individual tumour tissue cells located especially in the vicinity of blood vessels. When validating non-invasive fluorescence imaging, we found that this technique was not suitable for providing accurate estimates of experimental tumour volumes, but that it may be used for the semi-quantitative detection of tumour growth.

Although DPP-IV was increasingly expressed in highly malignant glial tumours, our work has shown that – in accordance with previous studies – DPP-IV likely exerts compensatory antitumour effects. Experiments employing the xenograft model indicate that less extensive tumour growth associated with the high transgenic expression of DPP-IV in

transformed glial cells does not depend on its enzymatic activity. In the GEM model, DPP4 was spontaneously expressed primarily by stromal cells. These observations suggest that the biological role of DPP-IV in various tumour compartments may differ.

Our results expand the existing body of knowledge regarding the role of DPP-IV in oncogenesis; understanding these processes is a prerequisite for its further utilization as well as for the recognition of the potential risks posed by the therapeutic uses of this molecule.