ABSTRACT

Proteolytic enzymes are known to contribute to the initiation, development and progression of a number of diseases. Dipeptidyl peptidase IV (DPP-IV) and fibroblast activation protein (FAP) are serine proteases with the unique ability to cleave dipeptides containing - highly evolutionarily conserved - proline at the penultimate position of the N-terminus of substrates/biologically active peptides. FAP also exhibits gelatinolytic activity, which it exerts during extracellular matrix remodeling processes. Glial brain tumors (gliomas) arise from resident transformed glial cells, whereas brain metastases originate from circulating transformed extracranial tumor cells. Our previous work has described an increased expression of DPP-IV and FAP in high-grade glioma tissues. The presence of DPP-IV and FAP in brain metastatic tissues has not been described to date.

The aim of this thesis was to describe the multiple forms of DPP-IV and FAP, and to describe their cellular origin and possible regulation in brain tumors. DPP-IV and its molecular MW and pI forms were expressed predominantly by transformed glial cells, whereas FAP and its MW and pI forms were expressed by transformed and stromal cells present in GBM and brain metastatic tissues. The spectrum of multiple forms of DPP-IV and FAP in GBM tissues and transformed glial cells was probably not a result of glycosylation.

We found a previously undescribed molecular form of FAP with a pI of 7,0-8,5 in GBM tissues and in brain metastases. In stromal cells, in contrast to transformed glial cells, several forms of FAP with pI 7.0-8.0 were found. Molecular forms of FAP with pI 7,0-8,5 can also be induced within glioma cells and non-tumor pericytes present in GBM tissues in the context of the tumor microenvironment. Expression of FAP, but not DPP-IV, was induced by TGF-β1 in glioma and stromal cells present in GBM tissues and in brain metastases.

Understanding the regulation of the expression of multiple forms of DPP-IV and FAP and their biological functions in the tumor microenvironment may contribute to the identification of additional therapeutically relevant targets in the treatment of brain tumors in the future.

Key words: dipeptidyl peptidase IV (DPP-IV), fibroblast activation protein (FAP), brain tumors, tumor microenvironment, TGF-β1.