Dipeptidyl peptidase-IV (DPP-IV, CD26, EC 3.4.14.5) is a widely expressed serine protease that by limited proteolysis regulates a number of biologically active peptides including a number of mitogenic peptides involved in cancer development. Deranged DPP-IV expression and/or enzymatic activity has been reported in a number of tumors, and could lead to altered signaling and biological function of its substrates.
Changes in DPP-IV expression were observed in glioma cell lines in association with differentiation, and recently also in malignant gliomas in vivo. In addition, DPP-IV substrates substance P (SP) and stromal cell derived factor-1 (SDF-1) that trigger growth promoting intracellular signaling cascades in glioma cells have strongly been implicated in the pathogenesis of gliomas.
The aim of this study was (i) to investigate the effects of DPP-IV on the signaling of its biologically active substrates that promote the malignant phenotype of glioma cells, and (ii) to assess the effects of DPP-IV on the growth, migration and adhesion of human glioma cells.
Using transfected glioma cell lines (U373CD26, T98GCD26, U87CD26) with mifepristone-inducible DPP-IV expression, we demonstrate that DPP-IV overexpressing T98GCD26 cells can cleave SP and thus abrogate its ability to trigger calcium signaling in U373 cells. (...)
SP increased the percentage of cells in S phase of the cell cycle in U373 glioma cells.
In conclusion, using transfected human glioma cells with inducible DPP-IV expression, we demonstrate that DPP-IV impairs the growth of glioma cells in vitro and is able to alter intracellular signaling cascades triggered by SP. Our data however suggest that cleavage of SP may be dispensable for the growth inhibitory effect of DPP-IV. Indeed, the results with a DPP-IV inhibitor Diprotin A imply that the effects of DPP-IV in glioma cells may involve nonproteolytic mechanisms.