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Title: Multifunctional proteases dipeptidyl peptidase-IV and fibroblast activation protein as possible pathogenetic factors, biomarkers and therapeutic targets in cancer

Summary:

Dipeptidyl peptidase-IV (DPP-IV, CD26) and fibroblast activation protein (FAP, seprase) are non-classical serine proteases belonging to S9B subfamily. Both enzymes cleave N-terminal X-Pro/Ala dipeptides from bioactive peptides, and FAP has also an endopeptidase activity. DPP-IV and FAP exhibit 52% identity at the amino acid level and are present as membrane-bound glycoproteins or in a soluble form in blood plasma. DPP-IV is broadly expressed in various tissues and cell types. In contrast, FAP is only scarcely present in adults under physiological conditions, but its expression is upregulated in states of tissue remodeling such as during embryonic development, in healing wounds, in chronic inflammation, and in cancer. DPP-IV has become more broadly known due to its ability to cleave incretins and due to the use of low molecular weight DPP-IV inhibitors (gliptins) for the treatment of type 2 diabetes mellitus (T2DM). Nevertheless both DPP-IV and FAP are thought to be involved in a number of other physiological and pathological states and processes by cleaving a variety of biologically active peptides and/or by "non-proteolytic" protein-protein interactions.

Our studies focused on DPP-IV and FAP in the context of two recalcitrant human malignancies, glioblastoma (GBM) and pancreatic ductal adenocarcinoma (PDAC). Expression of DPP-IV and FAP is increased in PDAC tissues compared to matched paired non-tumorous pancreatic tissue. We have further demonstrated that both proteases are co-expressed in human alpha cells in Langerhans islets under physiological conditions as well as in PDAC. Plasma levels of DPP-IV enzymatic activity are higher in PDAC with recent onset diabetes and weight loss compared to patients with T2DM without PDAC. Thus DPP-IV and FAP may be involved in the regulation of the endocrine pancreas and their deregulated expression in PDAC may possibly contribute to the frequent co-occurrence of PDAC and newly diagnosed diabetes mellitus.

The expression of DPP-IV and FAP in GBM is higher compared to non-tumorous brain. However, our studies have shown that forced expression of DPP-IV in glioma cells decreases their growth *in vitro* and *in vivo*, in large part independently of its enzymatic activity. FAP expression in glioblastoma is associated with the mesenchymal subtype of glioblastoma and correlates with the expression of genes encoding extracellular matrix proteins, factors involved in inflammation and wound healing, and several proteases. FAP is expressed in malignant, presumably non-stem cells in glioblastoma, and further in several types of stromal cells including perivascularly localized mesenchymal cells and a small subset of $CD45^+$ cells.

In a collaborative project, highly specific FAP targeting compounds based on a low molecular weight inhibitor (iBodies) were developed. Using the iBody concept, we are currently developing and in preclinical models testing potential novel anticancer FAP targeting compounds.

Taken together, our results along with other studies suggest that DPP-IV and FAP play a role in cancer pathogenesis. Available data also indicate that in certain cancers DPP-IV and FAP may represent useful biomarkers and potential therapeutic targets.

Selected publications:

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