

Targeting a stromal cell protease inhibits tumor growth

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Abstract

Tumors are collections of heterogeneous populations of cells including cancer cells and a multitude of stromal cells. Although the prevalence of various stromal cells varies between tumors, they include pericytes, fibroblasts, immune, inflammatory and vascular endothelial cells. Stromal cells have the ability to communicate among themselves as well as with cancer cells through direct cell contact and by secretion of growth factors, chemokines, proteases and deposition and remodeling of extracellular matrix (ECM). The stromal network is pivotal to the impact of the microenvironment on tumor initiation, progression and metastasis. Thus, stromal targets may provide opportunities to develop therapies that complement tumor cell targeted therapies. Among these potential targets, fibroblast activation protein (FAP, also called FAP α or seprase) has recently gained attention due to its tightly regulated expression in the tumor stroma and structurally-defined enzymatic activity.

FAP is a member of the dipeptidyl aminopeptidase family of serine proteases that also includes its dipeptidyl peptidase IV (DPP_{IV}/CD26). FAP is a type II transmembrane protein and has both dipeptidyl peptidase activity, which is shared by other members of the family, and endopeptidase activity including, collagenolytic activity capable of degrading gelatin and type I collagen. Although it has been suggested that FAP may have the potential to degrade ECM, the *in vivo* substrate(s) is still not defined. FAP is expressed in over 90% of common human epithelial cancers on cancer-associated fibroblasts, but not the cancer cells per se. Although also expressed in wound healing and other pathologic settings, (in particular chronic inflammation and fibrosis), FAP is not detected in benign tumors or normal adult tissues. Given the highly regulated expression and restricted distribution of FAP, lack of overt pathology in FAP-deficient mice, animal results suggesting that ectopic over expression of FAP promotes tumorigenesis and the correlation between high FAP expression and poor cancer prognosis, it has been suggested that FAP inhibition may be a useful target for cancer therapeutics.

We studied the impact of genetic deletion of FAP and pharmacologic inhibition of the enzymatic activities of FAP and CD26, on the growth of colon and pancreatic syngeneic transplanted tumors and in a K-ras^{G12D} driven endogenous lung tumor model in immunocompetent mice. We found that endogenous FAP expressed on tumor stromal cells promotes tumor progression in each of these models via its enzymatic activity and that deficiency in FAP resulted in an accumulation of collagen. Interestingly, although specific inhibition of CD26 activity did not affect transplanted colon or pancreatic tumor growth, it did have a negative effect on tumor growth in lung where CD26 is expressed on epithelial cells and infiltrating inflammatory cells. FAP promoted tumor growth by promoting

tumor cell proliferation, and was required for tumor stromagenesis and vascularization. These results suggest that inhibition of FAP enzymatic activity warrants further investigation for its potential therapeutic effect either alone or in combination with tumor cell targeted therapies.