Review

Expression Pattern of Dipeptidyl Peptidase IV Activity and/or Structure Homologues in Cancer

(dipeptidyl peptidase / fibroblast activation protein α / DASH / cancer)

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Abstract. Proline at the second position of the N-terminus of biologically active peptides involved in cell growth regulation is an evolutionarily conserved motif protecting them against cleavage by non-specific proteases. Just a small number of proline-specific hydrolases including dipeptidyl peptidase IV (DPP-IV) and related molecules is capable of cleaving such post-prolyl bond. DPP-IV, originally described on the basis of its enzymatic activity, is a ubiquitous, multifunctional homodimeric plasma membrane glycoprotein of type II. Subsequently, several other molecules related to DPP-IV by their enzymatic activity and/or sequence were discovered and classified as "dipeptidyl peptidase IV activity and/or structure homologues" (DASH). Along with canonical DPP-IV this group comprises DPP-IVβ, DPP-II, DPP6, DPP8, DPP9, DPP10 and fibroblast activation protein α (FAP-α). Recent observations of deregulated expression of several DASH molecules in multiple human cancers led to the assumptions of their pathogenetic relevance in cancerogenesis. Here we review recent information about selected DASH molecules in human malignancies.

Received November 14, 2008. Accepted January 23, 2009.

This study was supported by grant MSMT 0021620808.

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Abbreviations: ADA – adenosine deaminase, APCE – antiplasmin-cleaving enzyme, CD – cluster of differentiation, CIN – cervical neoplasia, CXCR – CXC receptor, DASH – dipeptidyl peptidase IV activity and/or structure homologues, DPP – dipeptidyl peptidase, ECM – extracellular matrix, ERK – extracellular signal-regulated kinase, FAP – fibroblast activation protein, FGF – fibroblast growth factor, HIV – human inmunodeficiency virus, IL – interleukin, MAPK – mitogen-activated protein kinase, Mig – monokine induced by interferon γ, MIP 1 – macrophage inflammatory protein 1, MW – molecular weight, NPY – neuropeptide Y, PYY – peptide YY, QPP – quiescent cell proline dipeptidase, RANTES – regulated upon activation, normal T-cell expressed, and secreted, SDF-1α – stromal cell-derived factor 1α, SP – substance P.

Introduction

Cancer is one of the leading causes of death in the world. Disrupted responsiveness to humoral growth regulators belongs to the typical features of tumour progression. Interestingly, a number of biologically active peptides controlling cell growth processes possess a proline residue at the second position of their amino-terminus (Vanhoof et al., 1995). Among them, neuropeptide Y (NPY), peptide YY (PYY), growth hormone-releasing hormone, substance P (SP), glucagon-like peptide 1,2, gastrin-releasing peptide, chemokines (regulated upon activation, normal T-cell expressed, and secreted (RANTES), eotaxin, stromal cell-derived factor 1α (SDF-1α), monokine induced by interferon γ (Mig)) and interleukins (IL-2, IL-6) are supposed to act in cancer growth regulation (Gorrell, 2005). Such structural characteristic participates in the relative stability of the respective peptide by protecting it against its unspecific degradation by common proteases.

Dipeptidyl peptidase IV, formerly described by Hopsu-Havu (Hopsu-Havu and Glenner, 1966) on the basis of its unique substrate specificity, was believed to be the only enzyme capable to cleave out X-Pro dipeptides from its substrates. Subsequently, further evidence confirmed a growing panel of molecules possessing DPP-IV-like enzymatic activity and varying structural similarity. This fact led to definition of a novel molecular group of multifunctional "dipeptidyl peptidase-IV activity and/or structure homologous" (DASH) molecules (Busek et al., 2004). The specific enzymatic activity of DASH molecules makes them act as regulatory elements of regulatory circuits, exploiting soluble growth mediators. Indeed, deregulation of some DASH molecules has been observed in a number of human tumours.

These observations caused a substantial leap of interest in DASH molecules as important actors in cancer

Table 1. Dipeptidyl peptidase IV (DPP-IV) and fibroblast activation protein α (FAP-α) in cancer tissues

Type of cancer	DPP-IV or FAP-α dynamics	Notes
Lung cancer	↑ DPP-IV[(j)]	
Follicular thyroid cancer	↑ DPP-IV[(d, m)]	
Endometrial cancer	↓ DPP-IV[(e)]	Grade dependent
Colon adenocarcinoma	↓ DPP-IV[(l)] ↑ FAP-α[(b, f)]	 Associated with tumour progression
Gastric cancer	↑ FAP-α[(h)]	
Ductal breast cancer	↑ FAP-α – cells of ductal breast cancer[(a)] ↑ FAP-α – cells of tumour stroma[(a)]	Associated with tumour progression Better survival of patients
Cervical cancer	↑ FAP-α[(c)]	
Melanoma	↓ DPP-IV, ↓FAP-α[(n, i)] ↑ FAP-α[(g)]	
Epithelial skin cancer	↑ FAP-α[(g)]	
Glioma	↑ DPP-IV, FAP-α[(k)]	Grade dependent

(a) Ariga et al., 2001; (b) Iwasa et al., 2005; (c) Jin et al., 2003; (d) Kehlen et al., 2003; (e) Khin et al., 2003; (f) Henry et al., 2007; (g) Huber et al., 2007; (h) Mori et al., 2004; (i) Rettig et al., 1993; (j) Sedo et al.,1991; (k) Stremenova et al., 2007; (l) Tan et al., 2004; (m) Tanaka et al., 1995; (n) Wesley et al., 1999

pathogenesis with possible consequences in both the diagnostic and therapeutic arena (Sedo et al., 2008). However, there is no trivial relation of DASH expression pattern and biological behaviour of a particular cancer type. According to the literature and to our own results as well, the DASH role may be pro- or anti-oncogenic within the particular cancer (Table 1). Such seeming contradiction may be explained by tumour type-specific local microenvironment (Chen, 1996; Cheng et al., 1998; Iwata and Morimoto, 1999; Wesley et al., 1999; Chen and Kelly 2003; Kajiyama et al., 2003; Wesley et al., 2005). Although several DASH molecules are believed to execute some of their biological functions also by non-hydrolytic mechanisms, this review will concentrate on the proteolytic aspects of DASH functions in cancer biology (Hanski et al., 1988; Subramanyam et al., 1993; Jacotot et al., 1996a; Sedo et al., 1996; Gonzales-Gronow et al., 2001; Weihofen et al., 2004).

DASH molecules

Dipeptidyl peptidase IV (DPP-IV, EC 3.4.14.5, T-cell activation antigen CD26)

DPP-IV (EC 3.4.14.5) is a type II transmembrane glycoprotein which consists of a large extracellular domain (C-terminus) connected by a flexible stalk region to a hydrophobic transmembrane domain and a short intracellular tail (N-terminus) (Engel et al., 2003; Lambeir et al., 2003).

Monomer of DPP-IV is a 110-kDa glycoprotein of 766 amino acids. Dimerization of DPP-IV (MW 240 kDa) is a prerequisite for its proper enzymatic activity. Interestingly, catalytically active heterodimers with fibroblast activation protein α (FAP-α) have been observed (Scanlan et al., 1994). There is also a soluble counterpart of DPP-IV, present in blood plasma and intracellularly. This molecular form lacks the transmembrane and intracellular part. It is typically present as a homodimer with MW 210–290 kDa, but can also form higher molecular complexes of 900 kDa (Lambeir et al., 2003).

DPP-IV typically cleaves Xaa-Pro or Xaa-Ala dipeptides from the N-terminus of peptides. This rare substrate specificity is therefore seen as crucial for functional regulation of bioactive peptides and their resulting signalling potential. Following DPP-IV processing, peptides become available to attack by less specific proteases. As mentioned above, DPP-IV regulates functional activity of many important mediators such as hormones, neuropeptides, cytokines and chemokines (Gorrell, 2005). On top of the biological roles derived from its proteolytic activity, DPP-IV also executes several functions by means of non-hydrolytic intermolecular interactions with adenosine deaminase (ADA) (Weihofen et al., 2004), plasminogen (Gonzales-Gronow et al., 2001), HIV envelope glycoprotein 120 (Jacotot et al., 1996b) and HIV transactivation protein (Tat protein) (Subramanyam et al., 1993). DPP-IV also interacts with proteins of extracellular matrix (ECM) such as collagen (Hanski et al., 1988) and fibronectin (Piazza et al., 1989; Yu et al., 2006), mediating the cell-ECM adhesion.

DPP-IV is expressed as a fully active enzyme. It is thought that expression of DPP-IV is regulated at the levels of gene expression, transcription and translation. Hepatocyte nuclear factor 1α has been shown to act as a DPP-IV transcription factor in human colon adenocarcinoma and hepatocellular liver carcinoma cell lines (Erickson et al., 1999).

DPP-IV is ubiquitously expressed on endothelial and epithelial cells, fibroblasts and lymphocytes. In several organs (e.g., cardiac, skeletal muscle), DPP-IV on the endothelium accounts for most of the enzymatic activity of their tissue. Interestingly, DPP-IV-positive neurons were found only in foetal brain, where their activity sub-

sided during subsequent development. In mature brain, DPP-IV is localized only in epithelial cells of vessels of the blood-brain barrier and on ependyma (Bernstein et al., 1987; Lambeir et al., 2003). Moreover, DPP-IV/CD26 is considered to be a marker of immune cell activation (Fleischer, 1994).

DPP-IV-like enzymatic activity is also present in blood plasma, cerebrospinal fluid and other body fluids. The majority of this activity is attributed to the soluble counterpart of canonical DPP-IV as mentioned above. The origin of this isoform remains unclear. It is speculated that it may arise by shedding from the plasma membrane of endothelial or epithelial cells, or from circulating lymphocytes by proteolytic cleavage of the original transmembrane molecule. It is supposed that serum DPP-IV inactivates circulating bioactive peptides, thus protecting the organism against their inappropriate systemic effects (Lambeir et al., 2003, Gorrell, 2005).

Fibroblast activation protein α (FAP-α, seprase)

Similarly to DPP-IV, FAP-α is a type II transmembrane glycoprotein with a length of 760 amino acids. Homodimerization (170 kDa) is necessary for its enzymatic activity (Goldstein et al., 1997). Compared to DPP-IV, FAP-α displays only one hundredth of post-proline dipeptidyl peptidase activity and substantialy differs in the expression pattern (Edosada et al., 2006a). Moreover, in contrast to DPP-IV, FAP-α possesses collagen type I-specific gelatinase activity toward the X-Gly-Pro-Y sequence providing the molecule with potential to participate in degradation of structural proteins of the extracellular matrix. Both endopeptidase and exopeptidase activities reside in a common active site in FAP-α (Bermpohl et al., 1998; Edosada et al., 2006b).

Tumour development is dependent on the formation of supportive tumour stroma. While FAP-α is almost absent in most of differentiated cells, it is abundantly expressed by tumour stromal fibroblasts in epithelial and mesenchymal tumours, as well as in melanomas. Thus, it is according to some authors implicated in ECM remodelling and involved in processes of cell adhesion, migration and invasion. Taken together, FAP-α is believed to be an important player in regulation of tumour growth and metastasizing (Monsky et al., 1994; Ariga et al., 2001; Jin et al., 2003; Ramirez-Montagut et al., 2004; Iwasa et al., 2005; Henry et al., 2007).

FAP-α has also been supposed to interact with DPP-IV, forming together a membrane-bound heterodimer (with increased dipeptidyl peptidase, gelatinase activity). These heterodimers were described on the cell surface of proliferating fibroblasts and melanocytes grown with fibroblast growth factor and phorbol ester *in vitro*. It has been suggested that DPP-IV/FAP-α heterodimers participate in cell growth regulation, differentiation, adhesion, migration, and metastasis of melanoma cells (Rettig et al., 1993; Ghersi et al., 2002).

Three alternative splicing forms of FAP-α have been described: 97 kDa seprase l ("long") with a small cytoplasmic domain, 50–70 kDa seprase s ("short") identical with the catalytic region, lacking the intracellular domain, of the long one, and 27 kDa isoform, lacking the active centre, located in the cytosol of melanoma cells (Goldstein et al., 2000).

FAP-α is typically expressed in foetal mesenchymal tissues. Although the FAP-α mRNA has been detected widely in adult tissues, the presence of FAP-α protein is normally restricted only to α-cells of pancreatic islets and endometrial cells. FAP-α production is considered to be linked to multiple pathological processes. It is strongly expressed by activated hepatic stellate cells in liver cirrhosis and by mesenchymal cells of remodelling tissue such as stromal fibroblasts of healing wounds, lung fibrosis and epithelial tumours (Garin-Chesa et al., 1990; Levy et al., 1999; Park et al., 1999; Dolznig et al., 2005; Gorrell, 2005).

The soluble form of FAP-α occurring in the blood plasma is identical to antiplasmin-cleaving enzyme (APCE). APCE converts α2-antiplasmin into a more active form and thus suppresses fibrinolysis. On the other hand, DPP-IV promotes fibrinolysis by association with ADA and plasminogen 2, which both enhance activity of plasminogen 2 (Lee et al., 2006).

Dipeptidyl peptidase-II (DPP-II, quiescent cell proline dipeptidase, QPP)

DPP-II is an intracellular serine protease localized in cell vesicles differing from lysosomes. Similarly to DPP-IV, homodimerization of DPP-II represents a prerequisite for its enzymatic activity. No physiological substrates of DPP-II have been described yet (Chiravuri et al., 2000, Leiting et al., 2003). Inhibition of DPP-II enzymatic activity causes atypical apoptosis of quiescent lymphocytes (Chiravuri et al., 1999).

Dipeptidyl peptidase 8 (DPP8), dipeptidyl peptidase 9 (DPP9)

DPP8 and DPP9 are considered to be evolutionarily the oldest enzymes with DPP-IV-like activity. Both are soluble proteins localized in the cytosol. In contrast to DPP-IV, monomers of DPP8 and also 9 represent the enzymatically active forms of the molecule. No natural substrates have been identified *in vivo* so far. DPP8 and DPP9 are widely distributed within various organs and tissues. The highest level of DPP8 was described in brain, testes and activated lymphocytes (Abbott et al., 2000). DPP9 was mainly detected in the liver, heart and skeletal muscle. DPP9 mRNA expression is abundant in leukocytic cell lines and various diseased and tumour-bearing tissues (Ajami et al., 2004).

Recent data showed that the DPP8 and 9 over-expression is associated with impaired cell adhesion, migration and cellular monolayer wound healing on collagen I, fibronectin and Matrigel. Further increase of DPP8, 9 has been proposed to induce apoptosis. Interestingly, all these functions are probably independent of the DPP-IV-like enzymatic activity (Yu et al., 2006).

Dipeptidyl peptidase 6 (DPP6, DPP X), dipeptidyl peptidase 10 (DPP10, DPP Y)

DPP6 as well as DPP10 lack DPP-IV-like enzymatic activity due to the mutation of their active site, where serine 630 residue is substituted by aspartic acid and by glycine, respectively. In human, both molecules are expressed mainly in the brain, where they participate in the modulation of A-type potassium channels in somatodendritic compartments of neurons. DPP6 also plays a role in neuronal development and synaptic plasticity (Strop et al., 2004).

Dipeptidyl peptidase IV-β (DPPIV-β)

DPPIV-β is a glycosylated monomer with DPP-IV-like enzymatic activity. In contrast to DPP-IV, DPPIV-β does not bind adenosine deaminase (ADA). This enzyme was detected in haematopoietic and lymphoid cells (Jacotot et al., 1996a).

Expression of DASH molecules in cancer

Deregulation of the DASH expression pattern was observed in a number of human tumours. There is experimental evidence suggesting a causal pathogenetic role in tumorigenesis in case of DPP-IV and FAP-α. However, on the basis of possible functional overlap caused by the common enzymatic activity, involvement of other DASH molecules in processes of cancerogenesis is also speculated, although the direct evidence is still missing. Thus, literature data dedicated to DPP-IV and FAP-α are reviewed below (Table 1).

Dipeptidyl peptidase IV

DPP-IV mRNA and protein levels are null or markedly reduced in non-small cell lung cancer cell lines. Re-expresion of DPP-IV on these cells resulted in morphological changes suggesting restoration of non-malignant phenotype, inhibition of cell proliferation and cell migration. Additionally, re-expression of DPP-IV was related to the increased expression of p21, which is involved in apoptosis and cell cycle arrest at the G1 stage (Wesley et al., 2004). Similarly, loss of DPP-IV expression was described in melanoma cells. Re-expression of DPP-IV in melanoma cell lines *in vitro* resulted in a change of cell phenotype into differentiated melanocytes (Wesley et al., 1999). Thus DPP-IV, acting as antioncogenic molecule in these systems, suppresses cell transformation, hence its downregulation could contribute to the loss of cell growth control.

In case of prostate carcinoma, *in vitro* experiments demonstrated a negative correlation between expression of DPP-IV and fibroblast growth factor 2 (FGF-2) in metastatic cells. FGF-2 is a powerful mitogen and its increased production is involved in tumour progression and metastasis of prostate carcinoma cells. Experimental re-expression of DPP-IV suppressed the malignant phenotype of prostate cancer cells by decreasing the levels of FGF-2 and reducing mediators of the FGF-2/MAPK-ERK1/2 signalling pathway, critical for survival and migration of tumour cells. DPP-IV re-expression also decreases levels of urokinase-type plasminogen activator (Wesley et al., 2005). At the tissue level, expression of DPP-IV is decreased and inversely correlates with tumour grade in biopsies from the endometrial carcinoma (Khin et al., 2003). Decline in expression of DPP-IV was also observed in tumours of the gastrointestinal tract. Moreover, increased levels of adenosine were measured in the hypoxic tumour focus of colon carcinoma. A high concentration of adenosine was related to decreased levels of DPP-IV and its enzymatic activity as well as to reduced binding of ADA and fibronectin. This process could alter anti-tumour immune response and facilitate invasion and metastasis of carcinoma cells (Tan et al., 2004).

Conversely, DPP-IV-like enzymatic activity and DPP-IV protein expression were up-regulated in thyroid cancer. This phenomenon was more pronounced in differentiated cancers compared to the anaplastic form (Tanaka et al., 1995; Kehlen et al., 2003). Accrual of DPP-IV expression observed in ovarian carcinoma is believed to induce up-regulation of E-cadherin and tissue inhibitors of matrix metalloproteinases. These effects were accompanied by loss of invasive potential of ovarian carcinoma cells (Kajiyama et al., 2003). In bioptic material from human astrocytic tumours, substantial up-regulation of DPP-IV and FAP-α expression associated with higher DPP-IV-like enzymatic activity, localized in both vascular and parenchymal compartments, was observed in high-grade gliomas (Stremenova et al., 2007). Interestingly, both DPP-IV mRNA and enzymatic activity up-regulation tightly correlated with expression of SDF-1α chemokine receptor CXCR4. This fact implies possible functional relevance: SDF-1α, the most potent pro-proliferative chemokine stimulating glioblastoma growth, represents one of the best DPP-IV substrates (Stremenova et al., 2007).

DPP-IV is also supposed to be involved in processes of breast cancer cell metastasizing. DPP-IV expressed on the surface of lung capillaries acts as a receptor for fibronectin, present on the surface of metastatic breast carcinoma cells. The soluble form of DPP-IV and monoclonal antibodies experimentally inhibited the DPP-IV-fibronectin interaction. It was proposed that the ability of many cancer cells to bind fibronectin from circulation may in turn enable their interaction with DPP-IV, suggesting a possible common mechanism of cancer cell metastasis to the lung (Cheng et al., 1998).

Fibroblast activation protein α

An antioncogenic activity of FAP-α was observed in studies on the LOX melanoma cell line. FAP-α restored contact inhibition and growth factor dependence of cells, both independent of its enzymatic activity (Rettig et al., 1993; Wesley et al., 1999; Ramirez-Montagut et al., 2004). However, co-localization of DPP-IV, FAP-α, matrix metalloproteinases and urokinase-type plasminogen activator on the invadopodias of melanoma cells has

been reported. It has been suggested that DPP-IV and FAP-α are responsible for the tissue-invasive phenotype and together with other proteases facilitate degradation of ECM, thus influencing cancer cell invasion and migration (Monsky et al., 1994).

FAP-α expression was observed in stromal fibroblasts in epithelial skin cancers of early stages. In fully developed basal cell carcinomas and squamous cell carcinomas, a gradient of FAP-α expression was noted, ranging from high expression in fibroblasts directly surrounding the tumour cells to a more diffuse pattern in the distal portion of the peritumoural stroma and no or scattered expression in the adjacent normal tissue. A similar gradient of FAP-α expression was found in melanoma metastases; moreover, FAP-α expression was noted even in uninvolved normal adjacent tissue. In melanocytic nevi weak-to-moderate expression of FAP-α was detected only in stromal fibroblasts (Huber et al., 2006).

Tumour stage- and size-dependent decrease of stromal FAP-α expression was found in colon cancer, suggesting that stromal FAP-α could be engaged in the early stages of the tumour development. In parallel, tumours with higher levels of stromal FAP-α expression were more prone to generalize. Thus, FAP-α has been suggested as a potential therapeutic target of earlier-stage tumours, aimed to disrupt FAP-α-driven tumour progression (Mori et al., 2004; Iwasa et al., 2005; Henry et al., 2007). In addition to stromal cells, increased levels of FAP-α were also observed in transformed epithelial cells of colorectal as well as gastric cancer parenchyma. FAP-α expression in these cases was associated with worse prognosis of the disease. Similarly, elevated levels of FAP-α were found in cancer cells and subepithelial stromal cells of microinvasive and invasive carcinoma of the cervix. In preinvasive cervical neoplasia (CIN1, 2, 3), no FAP-α-positive cells were detected. However, FAP-α was over-expressed in subepithelial cells of stage CIN3. Such FAP-α dynamics has been interpreted as an early event of cell invasion. Together, FAP-α might be considered as an early marker of local progression of cervical cancer (Jin et al., 2003). In astrocytic tumours, FAP-α transcription was WHO grade-dependent and supposed to participate in the observed increase of the overall DPP-IV-like enzymatic activity in the tumour tissue (Stremenova et al., 2007).

Interestingly, differing functional impact of FAP-α expression in ductal breast carcinoma has been observed depending on its cellular source within the tumour tissue. While in transformed epithelial cells elevated expression of FAP-α is associated with tumour progression and metastasizing, enhanced production of FAP-α in non-transformed stromal cells, adjacent to the tumour mass, is associated with longer patient survival (Ariga et al., 2001).

Conclusions

The group of DASH molecules comprises molecules possessing DPP-IV-like enzymatic activity and/or having a similar structure to the canonical DPP-IV. The broad biological potential of individual DASH members can be derived from their multifunctionality and differing cell-, tissue- or organ-specific roles. The most thorough information about the putative role of DASH in cancer biology collected so far concerns DPP-IV and FAP-α.

At the level of the transformed cell itself, loss of DPP-IV expression is mostly associated with cell transformation, while DPP-IV up-regulation is frequently associated with cell differentiation. Interestingly, restoration of DPP-IV expression in transformed cells may rescue the physiological appearance and behaviour of cells.

Up-regulation of DPP-IV within the cancer tissue was considered in some but not all types of tumours as a marker of more differentiated and less aggressive form of cancer. On the other hand, plasma membrane DPP-IV of lung epithelium could participate as a homing factor during metastasizing of cancer cells into the lung. A seeming contradiction coming from observations of up- or down-regulation of DPP-IV in some tumours could not be fully explained so far. However, it is worth mentioning that the cellular source of the DPP-IV expression within the tumour tissue remains mostly unclear. Hypothetically, due to its multifunctional, cell-specific repertoire, DPP-IV might in parallel facilitate some pro-oncogenic processes, e.g. neovascularization (Zukowska-Grojec et al., 1998), whilst at the level of the transformed cell itself it could play an anti-proliferative and thus anti-oncogenic role (Wesley et al., 1999; Ariga et al., 2001; Wesley et al., 2005). The resulting pro- or anti-oncogenic net effect probably depends on the broader context of the specific tumour. For example, it was observed that over-expression of DPP-IV in some tumours was associated with high expression of CXCR4, SDF-1α chemokine receptor. This mechanism could be seen as feedback facilitation of CXCR4-SDF-1α axis signalling as a compensation for SDF-1α cleavage by upregulated DPP-IV (Stremenova et al., 2007, Busek et al., 2008). Taken together, there is no trivial conclusion valid for all types of tumours about whether DPP-IV is a pro- or an anti-oncogenic molecule, but it seems highly probable that a broader context of cancer-specific local microenvironment should be considered to interpret experimental data.

Adult tissues display almost no expression of FAP-α. It was suggested that elevated FAP-α expression on stromal tumour cells or cells adjacent to the tumour focus could be a marker of early tumour stages. Its expression in malignant cells is associated with worse prognosis. Anti-oncogenic function of FAP-α, independent of its intrinsic enzymatic activity, was described in LOX melanoma cell lines. However, its co-localization with urokinase-type plasminogen activator in cell invadopodia was responsible for degradation of extracellular matrix as a condition of invasive phenotype.

Although the functional studies of DASH molecules are still at their beginning, so far accumulated knowl-

edge makes the group an extremely promising candidate for further diagnostic as well as therapeutic exploitation (Sedo et al., 2008).

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