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CD26/DPP4 - a potential biomarker and target for cancer therapy

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ABSTRACT

CD26/dipeptidyl peptidase (DPP)4 is a membrane-bound protein found in many cell types of the body, and a soluble form is present in body fluids. There is longstanding evidence that various primary tumors and also metastases express CD26/DPP4 to a variable extent. By cleaving dipeptides from peptides with a proline or alanine in the penultimate position at the N-terminus, it regulates the activity of incretin hormones, chemokines and many other peptides. Due to these effects and interactions with other molecules, a tumor promoting or suppressing role can be attributed to CD26/DPP4.

In this review, we discuss the existing evidence on the expression of soluble or membrane-bound CD26/DPP4 in malignant diseases, along with the most recent findings on CD26/DPP4 as a therapeutic target in specific malignancies. The expression and possible involvement of the related DPP8 and DPP9 in cancer are also reviewed.

A higher expression of CD26/DPP4 is found in a wide variety of tumor entities, however more research on CD26/DPP4 in the tumor microenvironment is needed to fully explore its use as a tumor biomarker. Circulating soluble CD26/DPP4 has also been studied as a cancer biomarker, however, the observed decrease in most cancer patients does not seem to be cancer specific. Encouraging results from experimental work and a recently reported first phase clinical trial targeting CD26/DPP4 in mesothelioma, renal and urological tumors pave the way for follow-up clinical studies, also in other tumor entities, possibly leading to the development of more effective complementary therapies against cancer.

Contents

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BCR/ABL1, breakpoint cluster region protein/Abelson murine leukemia viral oncogene homolog 1 fusion gene; CCL, C-C motif ligand; CLL, chronic lymphocytic leukemia; CFP, cyan fluorescent protein; CML, chronic myeloid leukemia; CRC, colorectal cancer; CP, chronic phase; CSC, cancer stem cell; CTCL, cutaneous T cell lymphoma; CXCL, C-X-C motif ligand; CXCR, C-X-C chemokine receptor type; DPP, dipeptidyl peptidase; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; ESFT, Ewing sarcoma family of tumors; FAP, fibroblast activation protein α; Gly-Pro-*p*NA, glycyl-prolyl-*para*-nitroanilide; HCC, hepatocellular carcinoma; HFD, high-fat diet; HSC, hematopoietic stem cell; IBD, inflammatory bowel disease; IL, interleukin; LSC, leukemic stem cell; mAb, monoclonal antibody; MM, multiple myeloma; MMP, matrix metalloproteinase; MPM, malignant pleural mesothelioma; NHL, non-Hodgkin lymphoma; NK cell, natural killer cell; NSCLC, non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; SCC, squamous cell carcinoma; sCD26/DPP4, soluble CD26/DPP4; TIL, tumor infiltrating lymphocyte; TNM, tumor node metastasis; TTT, time to treatment; T2DM, type 2 diabetes mellitus; USP22, ubiquitin-specific protease 22..

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1. Introduction

The discovery of dipeptidyl peptidase 4 (DPP4, DPPIV, CD26, adenosine deaminase binding protein, EC 3.4.14.5 (in the text DPP4 and CD26 are used interchangeably)) dates back more than 50 years ago but many questions about the regulation of its expression, function and role still need to be resolved. Initially, it was thought to be the only enzyme that could cleave off a dipeptide after a proline residue at the penultimate position at the N-terminus. However, throughout the years, more enzymes have been described with similar substrate preferences and/or structural similarities, such as DPP2 (DPP7, quiescent cell proline dipeptidase, EC 3.4.14.2), DPP8, DPP9 and fibroblast activation protein α (FAP, seprase, EC 3.4.21.B28). For this review, the main focus will be on CD26/DPP4 in cancer. To a lesser extent, DPP8 and DPP9 are also discussed as they have been implicated in cell death regulation. A substantial amount of work has been done on FAP in cancer. That topic has been extensively reviewed very recently (Puré & Blomberg, 2018) and is not elaborated here.

1.1. Dipeptidyl peptidase 4

CD26/DPP4 is expressed as a type II transmembrane protein, with a short six amino acid cytoplasmic tail. It is active as a dimer with a monomer molecular weight of 110 kDa. A soluble form, sCD26/DPP4, can be found in body fluids. It lacks the transmembrane region and serum sDPP4 starts at residue 39 (serine) (Durinx et al., 2000). The source of this sCD26/DPP4, however, is less well-defined. Sources that have been described include bone marrow-derived cells, skeletal muscle cells, vascular smooth muscle cells and adipocytes (Casrouge et al., 2018; Lamers et al., 2011; Raschke, Eckardt, Bjørklund Holven, Jensen, & Eckel, 2013; Zhendi Wang et al., 2014). The mechanism behind the release of CD26/DPP4 is currently unknown. To date, matrix metalloproteases, as well as kallikrein-related peptidase 5, have been implicated in the shedding (Nargis et al., 2017; Röhrborn, Eckel, & Sell, 2014). However, other findings point towards a potential secretion pathway for sCD26/DPP4, though possibly the secretion of another protease, which is needed for the shedding, was influenced (Casrouge et al., 2018). Most likely, the exact mechanism for release of CD26/DPP4 is dependent on the specific circumstances. The concentration and/or activity of this soluble form is often and easily measured in serum or plasma, making it an interesting biomarker candidate.

DPP4 is widely expressed in tissues with high expression in the kidney and small intestine. Additionally, it is expressed on endothelial and epithelial cells, and also on cells of the immune system (Lambeir, Durinx, Scharpé, & De Meester, 2003; The Human Protein Atlas, 2018b; Thul et al., 2017; Uhlen et al., 2015; Waumans, Baerts, Kehoe, Lambeir, & De Meester, 2015). Many peptides have been described that are cleaved by DPP4, including chemokines, neuropeptides and incretin hormones, and thereby changing their biological activity. Because CD26/DPP4 inactivates incretin hormones, CD26/DPP4 inhibitors have been used clinically for over a decade in type 2 diabetes mellitus (T2DM). Furthermore, DPP4 has multiple interaction partners, among which, but not exclusively, adenosine deaminase (De Meester et al., 1994; Kameoka, Tanaka, Nojima, Schlossman, & Morimoto, 1993) and caveolin-1 (Ohnuma et al., 2004). Interactions between DPP4 and the extracellular matrix have also been reported, although these may be indirect (H.-C. Cheng, Abdel-Ghany, & Pauli, 2003; Gorrell, Gysbers, & McCaughan, 2001; Löster, Zeilinger, Schuppan, & Reutter, 1995; Sato et al., 2005).

1.2. Dipeptidyl peptidase 8 and 9

In contrast to CD26/DPP4, DPP8 and DPP9 are intracellularly located enzymes. They are also active as a dimer. Due to their high structural resemblance, no selective inhibitors or substrates are currently available, complicating the research into their respective roles. However, since their discovery almost 20 years ago, a lot of progress has been made on their characterization. DPP8 and DPP9 are ubiquitously expressed and can be found in cells of the immune system, endothelia, brain, reproductive organs and others (Ajami, Abbott, McCaughan, & Gorrell, 2004; Dubois et al., 2009; Harstad et al., 2013; Maes et al., 2007; Matheeussen et al., 2011, 2013; Olsen & Wagtmann, 2002; Yu et al., 2009). Both have multiple isoforms, with the long isoform of DPP9 being targeted to the nucleus (Justa-Schuch, Möller, & Geiss-Friedlander, 2014). The first natural substrate of DPP9 to be identified was the $RU1_{34–42}$ antigenic peptide. Other substrates that have been found include calreticulin, adenylate kinase 2, and Syk (Justa-Schuch et al., 2016; Wilson et al., 2013). Interaction partners described to date include SUMO1 and H-Ras for DPP8 and DPP9 (Pilla et al., 2012; Yao et al., 2011), and filamin A, NLRP1 and CARD8 for DPP9 (Justa-Schuch et al., 2016; Zhong et al., 2018). Anti-inflammatory effects of the specific DPP8/9-inhibitor 1G244 have been described in human and murine macrophages (Matheeussen et al., 2013; Waumans et al., 2016). Additionally, DPP8/9-inhibitors have been reported to induce a lytic form of cell death, called pyroptosis, in murine and human macrophages (Johnson et al., 2018; Okondo et al., 2017, 2018; Taabazuing, Okondo, & Bachovchin, 2017; Zhong et al., 2018). The multiple articles on DPP8 and DPP9 in monocytes and macrophages clearly indicate a functional role in this cell type, however, further research is needed to put all the pieces of the puzzle together.

Since the excellent reviews by Šedo and Cordero (Cordero, Salgado, & Nogueira, 2009; Šedo, Stremenová, Bušek, & Duke-Cohan, 2008), a lot of new and exciting work on DPP4 and its closely related family members has been published in the cancer field. For CD26/DPP4, not only an update is given on its expression in tumors and cancer patients, but also its mechanistic role in primary tumors and metastasis is discussed. Whenever possible, we will highlight opportunities and open questions in the evaluation of its use as a biomarker or therapeutic target in cancer.

2. CD26/DPP4 expression and its role in primary tumors

CD26/DPP4 is mainly expressed on cells of various solid organs as well as on most hematopoietic cells (Fig. 1) (Gorrell et al., 2001; Mortier, Gouwy, Van Damme, Proost, & Struyf, 2016). Apart from this constitutive expression however, CD26/DPP4 expression is altered in numerous solid tumors such as gastrointestinal adenocarcinoma, lung cancer, mesothelioma and melanoma as well as in different hematologic malignancies. In this section, the focus is on intratumor CD26 expression. The circulating CD26/DPP4 levels (soluble as well as lymphocyte-bound) are discussed separately in a later section. As an exception to that principle, CD26 expression in all compartments is discussed here for the hematological malignancies. The importance of $CD26^+$ tumor-infiltrating lymphocytes is becoming clearer recently and is therefore covered in a separate section.

2.1. Hematological malignancies

Since Feller et al. investigated the DPP4 enzymatic activity in acute T-lymphoblastic leukemia in 1980 (Feller & Parwaresch, 1980), the expression of CD26/DPP4 has been shown for different hematological malignancies and research has begun to unravel its potential as a

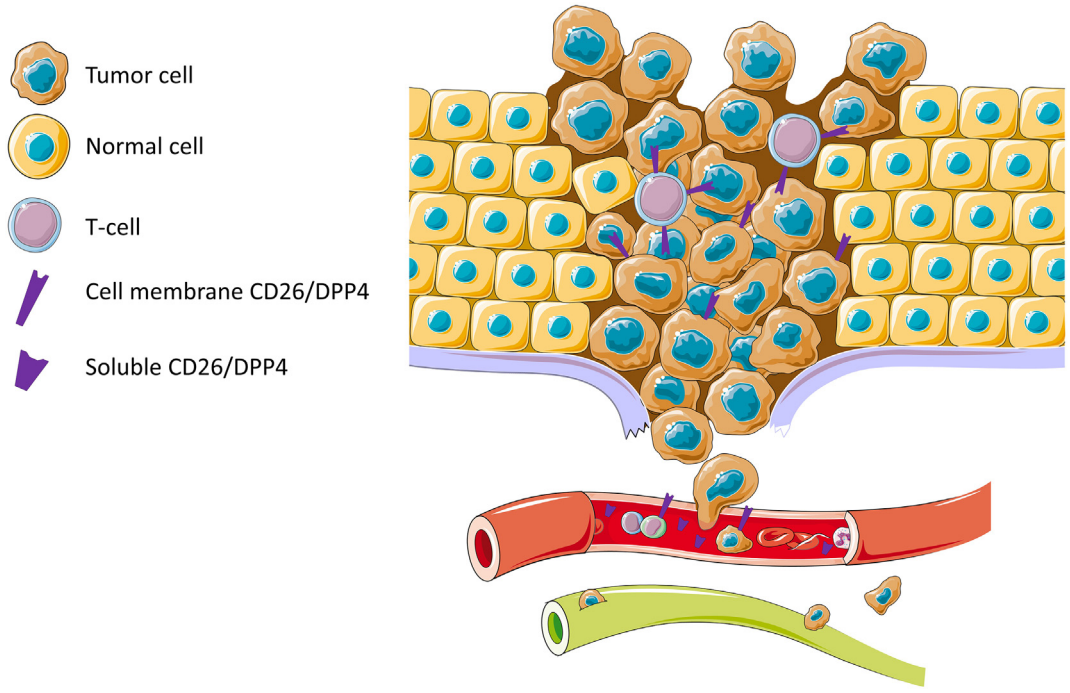

Fig. 1. Expression of CD26/DPP4 in cancer patients. CD26/DPP4 can be expressed on the surface of tumor cells and tumor-infiltrating immune cells. Some normal tissues also express CD26/DPP4 (for clarity not shown). In the circulation, it is found as a soluble form (sCD26/DPP4) and on the surface of immune cells.

therapeutic target and most noteworthy, as a cancer stem cell marker in cancer of the hematopoietic system.

In acute leukemia samples, including acute T-, B-lymphocytic leukemia (T-, B-ALL) and acute myeloid leukemia (AML), CD26 cell membrane expression was comparable with samples from non-leukemia patients (De Andrade, Bigni, Pombo-De-Oliveira, Alves, & Pereira, 2009). However, plasma sCD26/DPP4 activity was higher in leukemia patients and in non-leukemia patients with hematological alterations compared to normal controls. The specificity of the assay was confirmed with the specific DPP4 inhibitor sitagliptin, an inhibitor more specific to DPP4 than e.g. vildagliptin. DPP4 activity in plasma showed a significant direct correlation with CD26/DPP4 expression on immune cells in T-ALL, while an inverse correlation was seen in B-ALL (De Andrade et al., 2009). In contrast to these findings, in vitro data on T-ALL cell lines CEM and MOLT3 could not establish any correlation between CD26/DPP4 expression and soluble DPP4 activity in the culture medium (Dourado et al., 2007).

The expression of CD26/DPP4 in chronic lymphocytic leukemia (CLL) has been extensively published, especially in B-lymphocytic CLL (B-CLL). Flow cytometric analysis of CD26 protein expression (Cro et al., 2009; Hodeib & Shahbah, 2016) as well as microarray based gene expression (Carlucci et al., 2009) both confirmed the earlier described overexpression of CD26 in B-CLL (Bauvois, Dumont, Rouillard, Zhao, & Bosmans, 1999).

When investigating CD26 expression as a prognostic marker for B-CLL, it was found to correlate with known prognostic factors, clinical stage of disease, tumor mass, time to treatment (TTT), overall survival as well as disease free survival, strongly suggesting it as a negative prognostic biomarker as well as a marker in the risk assessment of B-CLL patients (Cro et al., 2009; Hodeib & Shahbah, 2016; Matuszak et al., 2016). Cro et al. studied the CD26/DPP4 expression of different B-cell lymphoid tumors in peripheral blood samples, among them B-CLL, $CD5^{neg}$ B-cell chronic lymphoproliferative disease and hairy cell leukemia (Cro et al., 2009). A large variation in the CD19-positive neoplastic B-cells expressing CD26 was observed. Significant correlations were found between the expression of CD26/DPP4 and CD49d, CD38, ZAP-70, FISH abnormalities and IgVH mutational status in B-CLL patients. In this cohort, $CD26/DPP4^-$ cases had a significantly longer TTT compared to $CD26/DPP4^+$ patients, indicating that CD26/DPP4 could be used in a prognostic model. Soluble CD26/DPP4 levels were not significantly different in serum samples of B-CLL patients in Binet stage A compared to healthy controls (Molica et al., 2009). Nonetheless, use of a cut-off value for sCD26/DPP4 levels identified two subsets of patients with a different clinical outcome regarding TTT. Patients with higher levels of sCD26/DPP4 were in earlier need of therapy. In addition, combination of sCD26/DPP4 levels with IgVH mutational status also identified multiple groups with differences in TTT, suggesting that sCD26/DPP4 levels can be used to predict the clinical outcome of patients with early B-CLL (Molica et al., 2009).

Matuszak et al. found that CD26/DPP4 expression increased according to Rai clinical stage and that it was significantly higher in patients with elevated lactic acid dehydrogenase serum activity or elevated serum β2-microglobulin concentration. In addition, a correlation between CD26/DPP4 expression and absolute lymphocyte count was seen at the time of diagnosis. Altogether, these results suggest that CD26 expression on B-CLL cells reflects the tumor mass. Moreover, CD26/DPP4 expression was found to be an independent prognostic variable of TTT, with patients in the $CD26^-$ group having a longer TTT compared to patients in the $CD26^+$ group (Matuszak et al., 2016). In their case-control study performed in 75 patients diagnosed with B-CLL, the CD26/DPP4 overexpression correlated positively with white blood cell count, absolute lymphocyte count and Rai's clinical stage of disease. Moreover, CD26/DPP4 expression correlated with shorter overall survival and disease-free survival (Hodeib & Shahbah, 2016).

Several studies examined cell-bound CD26 expression and sCD26 in serum of patients with cutaneous T cell lymphoma (CTCL), a form of non-Hodgkin lymphoma with heterogeneously characterized subgroups (Narducci et al., 2006). Recently, a study performed on patients with transformed mycosis fungoides, a particularly aggressive phenotype among the CTCL, suggested a loss of CD26 on $CD4^+$ T cells as a predictor of poor prognosis (Vural et al., 2017). This finding complements the result of a previous study showing that serum CD26 levels were significantly lower in patients with mycosis fungoides compared with normal controls (Miyagaki et al., 2013). Contrasting these findings, a retrospective cohort analysis examining the fraction of $CD26^-$ $CD4^+$ T cells as a marker for therapy response in 11 patients with erythrodermic CTCL revealed that CD26 expression on $CD4^+$ T cells was not a reliable marker for therapy response or disease progression (Vandersee et al.,

2015). However, considering the small sample size of 11 patients, this observation should be repeated in a larger patient cohort. As mentioned above, Miyagaki et al. detected a decreased sCD26/DPP4 protein level in serum CTCL patients (38 mycosis fungoides and 6 Sézary syndrome) compared to healthy controls and patients with atopic dermatitis (Miyagaki et al., 2013). However, patients with psoriasis also showed decreased levels. Furthermore, there were significantly lower serum levels in patients with advanced stage of CTCL compared to early stage CTCL. An inverse correlation was also found between sCD26/DPP4 levels and serum eotaxin, eotaxin-3 and cutaneous T cell attracting chemokine levels, which are correlated with disease severity. Because sCD26/DPP4 alone is not enough to differentiate between CTCL and psoriasis, another parameter, thymus and activation-regulated cytokine, was added and this combination was helpful in the diagnosis of atopic dermatitis, CTCL and psoriasis. Likewise, a decreased plasma sCD26/DPP4 activity was described in patients with CTCL (11 Sézary syndrome patients and 7 mycosis fungoides patients) compared to controls (Narducci et al., 2006). Similarly, another study examining sCD26/DPP4 activity in serum, expression on lymphocytes and total white blood cells in different hematological malignancies, including non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, leukemia (including patients with AML, ALL and CLL), plasmacytoma and multiple myeloma (MM), reported a decrease in enzymatic activity in NHL, leukemia and MM (Matić et al., 2013). In addition, a decrease in the percentage of $CD26^+$ lymphocytes has been observed in NHL and leukemia. The percentage of $CD26^+$ total white blood cells was reduced in patients with NHL and MM. CD26/DPP4 is incorporated in two validated Euroflow panels for immunophenotyping of hematological malignancies. In one of them, CD26/DPP4 was added as a marker of T cell chronic lymphoproliferative diseases for the identification of Sézary cells, which typically show $CD26^-$ T cells (Bernengo et al., 2001; Jones, Dang, Duvic, Washington, & Huh, 2001; Kelemen, Guitart, Kuzel, Goolsby, & Peterson, 2008; Novelli et al., 2015; Sokolowska-Wojdylo et al., 2005; Van Dongen et al., 2012). CD26/DPP4 is also a marker in a second panel applied in natural killer (NK) cell chronic lymphoproliferative diseases. It was included because under normal circumstances, CD26/DPP4 is not, or lowly, expressed on NK cells while it is present on pathological NK cells in some rare cases (Van Dongen et al., 2012).

In the T-anaplastic large cell lymphoma cell line Karpas 299, CD26 led to increased cell adhesion via fibronectin and ß1-integrin (Sato et al., 2005). Furthermore, CD26 depletion revealed that CD26 expression leads to an upregulated expression of versican on T cells, which is known to bind several extracellular matrix (ECM) components and cell-surface proteins, including fibronectin and integrin ß1 (Havre et al., 2013). Another in vitro study found that CD26 increased stromal cell-derived factor 1-alpha or C-X-C motif ligand (CXCL)12 on T cell lines, thus increasing their invasion capability. Phosphoinositide 3-kinase and mitogen-activated protein kinase 1 pathways as well as CD45 (Havre et al., 2009, 2013) were potentially involved. In vivo, CD26-depleted tumor cells showed no tumorigenicity and thus led to longer survival of the mice (Sato et al., 2005). Interestingly, CD26 surface expression, which correlated with adenosine deaminase expression, was found in several cases of anaplastic lymphoma kinase-positive anaplastic large cell lymphoma and Hodgkin lymphoma. Corresponding with the findings discussed above, this study suggests a potential negative prognostic impact of CD26 expression in these patients (Kameoka et al., 2006). Taken together, these findings show that CD26 functions as a marker for tumorigenesis in T-anaplastic large cell lymphoma and potentially, as a prognostic marker.

Hematopoietic stem cells (HSCs) physiologically reside in vascular niches in the bone marrow. In leukemia however, these niches are remodeled and degraded, thus losing their ability to sustain HSCs while providing the environment for leukemic stem cells (LSCs) that ultimately compete with the HSCs in the bone marrow (Duarte et al., 2018). Current research has focused on LSCs, because interactions between leukemic cancer cells with their surrounding microenvironment in the bone marrow is associated with cancer development, resistance against chemotherapy and relapse (Hawkins et al., 2016). Examining markers eligible for the diagnostic separation of LSCs from HSCs, Herrmann et al. first identified CD26 as a new marker of $CD34^+/CD38^-$ stem cells in breakpoint cluster region protein/Abelson murine leukemia viral oncogene homolog 1 fusion gene-positive ($BCR/ABL1^+$) chronic myeloid leukemia (CML) (Herrmann et al., 2014). CD26 also showed relevance as a therapeutic target. However, CD26 was not expressed consistently in other myeloid malignancies, except in lymphoid blast crisis of CML, BCR/ABL1 p210 fusion protein-positive ($BCR/ABL1p210^+$) ALL and single cases of acute myeloid leukemia (Valent et al., 2014). Recently, Blatt et al. found that CD26 was expressed on LSCs of the Philadelphia chromosome-positive ALL subtype BCR/ABL1p210, qualifying as a diagnostic marker in the differentiation of LSC subtypes in combination with other partially expressed markers such as CD25 and interleukin (IL)-1 receptor accessory protein precursor (Blatt et al., 2018). While most other studies in this field investigate the expression in bone marrow, one more recent report focused on the expression of CD26/DPP4 on $CD45^+/CD34^+/CD38^-$ stem cells specifically in peripheral blood using flow cytometry (Bocchia et al., 2018). Firstly, this study assessed $CD26^+$ LSCs in all 120 newly diagnosed chronic phase (CP-) CML patients. Secondly, in 236 CP-AML patients on first-line treatment with tyrosine-kinase inhibitors, 71.6% of the patients still showed detectable $CD26^+$ LSCs in peripheral blood, but the expression was lower when compared to the cohort at diagnosis, while in 28.4% of the patients, $CD26^+$ LSCs were undetectable. Thirdly, in treatment-free remission patients, 74 of 112 patients still showed detectable $CD26^+$ LSCs, although these were again lower compared to patients at diagnosis. Moreover, there was a significant inverse correlation between the number of circulating $CD26^+$ LSCs and the duration of treatment-free remission. Many questions still remain, such as the dynamics of $CD26^+$ LSCs in peripheral blood during treatment and the possibility of a LSC threshold determining treatment-free remission (Bocchia et al., 2018).

In conclusion, CD26/DPP4 expression showed both a prognostic and diagnostic relevance in hematological malignancies. In B-CLL, overexpression of CD26/DPP4 is a negative prognostic biomarker, which correlates with tumor mass (Matuszak et al., 2016) and clinical disease stage (Hodeib & Shahbah, 2016). Additionally, higher sCD26 levels in patients predicted lower TTT, and sCD26 levels combined with IgVH mutational status predicted clinical outcome in early disease stages (Molica et al., 2009). Loss of CD26 expression on $CD4^+$ T cells might predict poor outcome in CTCL (Vural et al., 2017), however, CD26 expression on $CD4^+$ T cells was not found to be a reliable marker for therapy response (Vandersee et al., 2015). Moreover, sDPP4 activity was decreased in CTCL patients, and thus it could a possible marker for disease severity (Miyagaki et al., 2013; Narducci et al., 2006). Similar findings were also reported for NHL, leukemia and MM (Matić et al., 2013). Concerning its diagnostic value in hematological malignancies, CD26/DPP4 was included in two validated Euroflow panels, one for the immunophenotyping of T cell chronic lymphoproliferative diseases identifying Sézary cells and in another panel for NK cell chronic lymphoproliferative diseases (Van Dongen et al., 2012). In T-anaplastic large cell lymphoma, CD26 plays a role in tumorigenesis and shows potential as a prognostic marker.

Interestingly, CD26 has been identified as a CSC marker in $BCR/ABL1^+$ CML (Herrmann et al., 2014), lymphoid blast crisis of CML, $BCR/ABL1p210^+$ ALL and in single cases of acute myeloid leukemia (Blatt et al., 2018; Valent et al., 2014). Additionally, a significant inverse correlation between the number of circulating $CD26^+$ LSCs and the duration of treatment-free remission was found, suggesting the prognostic relevance of $CD26^+$ LSCs (Bocchia et al., 2018).

2.2. Skin tumors

2.2.1. Melanoma

CD26 is highly expressed in normal melanocytes, whereas it is downregulated during the malignant transformation to melanoma cells (Havre et al., 2008; Wesley, Albino, Tiwari, & Houghton, 1999).

In human melanoma cell lines that express CD26 comparably to melanocytes, analysis of an invasion assay revealed that the invasion of DPP4 transfected cells was reduced by over 75%. In a melanoma cell line (LOX), independent mutagenesis proved that neither the peptidase activity nor the cytoplasmic domain of CD26 was responsible for the loss of invasiveness. Rather, a possible mechanism could be that FAP, which is expressed in melanoma cell lines, might form pro-invasive homodimers in the absence of CD26/DPP4 (Pethiyagoda, Welch, & Fleming, 2000). The downregulation of CD26 was shown to occur at RNA level in eight out of ten melanoma cell lines, due to promoter methylation (McGuinness & Wesley, 2008). Furthermore, the long noncoding RNA SPRIGHTLY was found to be upregulated in human melanoma cells, which led to a downregulation of CD26/DPP4 gene expression (Zhao et al., 2016). All in all, these findings suggest an anti-oncogenic role of CD26 in melanoma. Due to the downregulation of CD26/DPP4 during malignant transformation, induction of CD26 expression poses a potential therapeutic target.

2.2.2. Squamous cell cancer of the skin

Limited research has been done on skin squamous cell carcinoma (SCC). One study on CD26 expression in SCC of the skin revealed CD26 expression to be significantly increased compared to seborrheic keratosis, but not in normal skin samples. One finding of note was the higher expression in peritumoral stroma than in tumoral stroma of SCC, in line with research on SCC in other cancer entities (Kacar et al., 2012). Since this study analyzed the CD26 expression in tumoral and peritumoral stroma, tumor infiltrating lymphocytes (TILs) might have contributed to positivity. However, tissues were not analyzed separately for TILs.

2.3. Brain tumors

DPP4 expression has been previously reported in the endothelium of capillaries in the plexus choroideus and in leptomeningeal cells (Mitro & Lojda, 1988). Changes in DPP4 enzymatic activity can occur in malignant transformation (Mentlein, 1999). Interestingly, Stremenova et al. reported that DPP4-like activity in healthy brain tissue is largely due to the DPP4-related enzymes DPP8/9 whereas in human glioma, it is caused by an upregulation of CD26/DPP4. The expression of DPP8 and DPP9 will be discussed in detail in a later section. The upregulation of CD26/DPP4 correlated with tumor grade (Stremenová et al., 2007). One possible explanatory mechanism might be that DPP4 is involved in the regulation of CXCL12 induced tumor growth. The chemokine CXCL12 stimulates growth of glioma cells and is cleaved by DPP4. An upregulation of C-X-C chemokine receptor type (CXCR)4, the receptor for CXCL12, was observed in parallel with an increased DPP4 expression and activity. On the one hand, this could mean that increased DPP4 expression leads to an upregulation of the receptor of CXCL12 promoting tumor growth (Stremenová et al., 2007), on the other hand, because DPP4 degrades CXCL12 (Zhong & Rajagopalan, 2015) causing an anti-oncogenic effect in glioma cells, the upregulation of CXCR4 paralleling CD26 expression might be compensatory.

In favor of the anti-oncogenic role of DPP4 in brain tumors, the same research group established that DPP4-like activity and expression of the proliferation marker Ki67 were negatively correlated in most glioblastomas. Moreover, patients with a low DPP4 activity level showed shorter survival (Mareš et al., 2012).

Similarly to CXCL12, substance P is possibly involved in glioma tumor growth and invasion (Busek, Stremenová, Krepela, & Sedo, 2008). Providing further evidence that CD26/DPP4 is involved in the inactivation of mediators promoting growth of glioma cells, Busek et al. showed that the pre-incubation of substance P with DPP4 overexpressing glioma cells resulted in substance P inactivation (Busek et al., 2008). In a follow-up study, it was shown that DPP4 expression was associated with reduced glioma growth and proliferation in vitro and a suppression of glioma growth in vivo. It was hypothesized however, that DPP4 interferes with several aspects of the malignant glioma growth, largely in an enzymatic activity-independent manner (Busek et al., 2012).

In contrast to findings in other tumor entities, CD26/DPP4 seems to play an anti-oncogenic role in human glioma. In consequence, similar to the findings in melanoma, CD26/DPP4 induction presents a potential therapeutic option.

2.4. Thyroid cancer

Since the overexpression of CD26/DPP4 in thyroid cancer was first described by Kotani et al. in 1991 (Kotani et al., 1991), research has focused on its potential as a diagnostic tool for thyroid neoplasms. DPP4 immunostaining of thyroid specimens was able to distinguish thyroid cancer from benign thyroid tumors such as follicular adenoma, adenomatous goiter and Hashimoto thyroiditis (Aratake et al., 1991), in particular follicular carcinoma from follicular adenoma (Iwabuchi et al., 1996; Kotani et al., 1992). CD26/DPP4 expression was also evaluated as a diagnostic marker in specimens of fine-needle aspiration cytology, with one study showing most diagnostic value in cases of papillary carcinoma (Kholová, Ryška, Ludvíková, Čáp, & Pecen, 2003) and in contrast, de Micco reporting 100% specificity for thyroid malignancies across different thyroid cancer subtypes (De Micco, Savchenko, Giorgi, Sebag, & Henry, 2008). Moreover, CD26/DPP4 was included in a three-gene panel that distinguished benign from malignant thyroid nodules (Zheng et al., 2015). In addition to being a useful diagnostic tool in the differentiation of malignant from benign thyroid nodules as well as the histological subtypes, CD26/DPP4 has recently been investigated as a potential target in therapy of thyroid cancer (Fröhlich, Engel, & Wahl, 2011; Lee et al., 2017).

2.5. Lung cancer

Lung cancer is the leading cause for cancer-related deaths in males worldwide and in females in more developed countries (Torre et al., 2015). Lung neoplasms are divided into the main histological subtypes, small cell lung cancer and non-small cell lung cancer (NSCLC) which entails the histological entities adenocarcinoma and SCC of the lung. CD26 expression in the human respiratory system was recently described in surface epithelium of the lower respiratory tract, serous cells of submucosal glands, in type 1 & 2 pneumocytes, alveolar macrophages, vascular endothelial cells and pleural mesothelium (Meyerholz, Lambertz, & McCray, 2016).

Analysis of DPP4 expression in vitro in human NSCLC cell lines H28, H226 and H441 revealed a reduction or even absence of DPP4 expression on mRNA and protein level in all NSCLC cell lines (Wesley, Tiwari, & Houghton, 2004). Upon restoration of DPP4 expression in DPP4-transfected SK-LUC-8 NSCLC cells, cell proliferation, in vitro cell migration and in vivo tumorigenicity in a mouse model were decreased, promoting a potential anti-oncogenic function of CD26/DPP4 in NSCLC. These results are in support of a previous study that linked a downregulation of CD26/DPP4 with the malignant transformation of melanocytes (Morrison, Vijayasaradhi, Engelstein, Albino, & Houghton, 1993).

Contrarily, analysis of DPP4 activity in the different histological subtypes of NSCLC revealed relevant differences among the histological subtypes. Using in vitro human cell lines A549 for adenocarcinoma and SK-MES-1 for SCC, Dimitrova et al. revealed that lung adenocarcinoma expressed CD26 on the cell surface, in contrast to lung SCC. DPP4 activity was higher in the fetal-derived human lung cell line compared to the adenocarcinoma or SCC line (Dimitrova et al., 2012), although these differences could be partly due to higher CD26 expression in lungs during embryonic development (Křepela et al., 1985). Additionally, the substrate used in this study, 4-(glycyl-L-prolyl hydrazido)-N-hexyl-1,8-naphthalimide as well as the applied inhibitor (N-(H-Phe-Pro-)-O-(4-nitrobenzoyl)hydroxylamine hydrochloride) are not DPP4 specific. This issue has been discussed in more detail in a previous review article (Vliegen, Raju, Adriaensen, Lambeir, & De Meester, 2017). Moreover, we measured DPP4-like activity in the A549 cell line and found that

almost all activity could be attributed to DPP8/9 as it was sensitive to inhibition with the selective DPP8/9-inhibitor 1G244 (own unpublished data). Analyzing our own cohort of patients, we found a four-fold increase of DPP4 activity in tissue samples of lung adenocarcinoma patients when compared to normal lung tissue (unpublished data). When inhibiting the activity of CD26/DPP4 in an experimentally set-up of subcutaneous murine tumor model using Lewis lung carcinoma and a human lung adenocarcinoma cell line, we obtained a significant reduction of tumor growth (Jang et al., 2017). Collectively, the available data on the expression of CD26 in lung cancer point to a high clinical relevance of CD26 as a potential therapeutic target.

2.6. Malignant pleural mesothelioma

Immunohistochemical analysis of seven tissue samples obtained from mesothelioma patients showed that CD26 is highly expressed in malignant mesothelioma cells as opposed to benign mesothelial cells (Inamoto et al., 2007), whereas CD26 expression in a larger sample size of 79 mesothelioma patients revealed CD26 expression in the majority of epithelioid and biphasic types, but a lack thereof in the sarcomatoid type (Aoe et al., 2012). While surface expression of CD26 is lacking, a study validating different antibodies for CD26 staining in mesothelioma reported cytoplasmic CD26 expression in all histological subtypes (Amatya et al., 2011). In fact, similar to findings in colon cancer cells, membrane-bound CD26 expression was upregulated upon confluence of malignant mesothelioma cells (Abe et al., 2011).

In vitro and in vivo experiments identified the cytoplasmic region of CD26 as relevant for tumor growth. CD26 associated with somatostatin receptor 4, one of five somatostatin receptors, which is known to induce apoptotic effects in cancer cells. Association with CD26 inhibited these cytostatic effects in mesothelioma cells. More importantly, epithelioid and biphasic mesothelioma specimens co-expressed both markers, strongly suggesting a combined targeting of these molecules in therapy (Yamamoto et al., 2014).

Aside from CD9 and CD24, CD26 was identified as a cancer stem cell (CSC) marker in malignant mesothelioma cell lines that were established from surgical specimens. $CD9^+$ and $CD24^+$ cells showed increased tumor formation in vitro and in vivo (Ghani et al., 2011). Interestingly, the expression of CD24 correlated with the expression of CD26 in sarcomatoid cell lines suggesting that targeting CD26 in therapy might affect $CD24^+$ CSCs in this mesothelioma subtype (Ghani et al., 2011).

A more recent in vitro study focusing on the interaction of the mesothelioma CSC markers CD9 and CD26 linked CD26 with increased invasive capability, opposed to CD9. CD26-induced invasiveness was mediated through interaction with α5ß1 integrin, identified via co-precipitation (Okamoto et al., 2014). Further investigating this interaction with integrin adhesion molecules, it was found that CD26 causes malignant pleural mesothelioma (MPM) cells to increasingly secrete periostin via tyrosine kinase Src-phosphorylation-induced nuclear translocation of the transcription factor Twist-related protein 1 (Twist1). Periostin in the culture medium of MPM cells increased cell migration and invasion (Komiya et al., 2014).

CD26 has also been shown to be a potential marker for chemotherapy response and a therapeutic target in malignant mesothelioma. Firstly, although there was no correlation with survival time, CD26 expression was linked to chemotherapy susceptibility and was significantly associated with a better prognosis in patients administered non-pemetrexed regimens. In vitro data revealed a high proliferation rate in mesothelioma cells highly expressing CD26, potentially causing a susceptibility to chemotherapy (Aoe et al., 2012).

Moreover, the role of CD26 has been investigated most thoroughly in malignant mesothelioma, discovering the pro-oncogenic function of CD26, its relevance as a prognostic marker and above all, targeting CD26 in a first-in-human phase I clinical study has shown promising results (Angevin et al., 2017), as discussed later on in this review.

2.7. Gynecologic malignancies

2.7.1. Breast cancer

CD26 expression and its function in primary breast cancer has yet to be thoroughly investigated, as previous research focused on metastatic breast cancer (Havre et al., 2008; Shingu et al., 2003). Nonetheless, more recent studies have begun to unravel the role of CD26 in primary breast cancer. Two studies investigated the immunophenotype of breast cancer cells, including surface expression of CD26 (Donnenberg et al., 2018; Leccia et al., 2012). Cell suspensions of human breast cancer cell cultures and reference breast cancer cell lines were analyzed by flow cytometry, where CD26 was found to be heterogeneously expressed in the different patient samples and the cell lines studied. CD26 expression analyzed in cell cultures of tumor specimens obtained from different histological subtypes was found at 69.8% in invasive lobular carcinoma ($n = 1$) and quite heterogeneously with an expression percentage between 2.6% and 74.2% in early stage invasive ductal carcinoma ($n = 6$) (Leccia et al., 2012). Considering the limited sample size, follow-up data on the CD26 expression in histological subtypes of breast cancer would be of interest.

Donnenberg et al. characterized surface markers of metastatic breast cancer cells obtained from malignant pleural effusion, stromal cells, breast cancer cell lines (MCF7, MDA-MB-231, and BT-474) as well as a model for malignant transformation and the development of an invasive cancer stem cell phenotype. This model consists of human mammary epithelial cells, immortalized HMLER cells, which are tumorigenic but non-invasive, HMLER cells transduced with transcription factor Twist that are invasive and exhibit mesenchymal-like characteristics in culture (Donnenberg et al., 2018). Epithelial-to-mesenchymal transition (EMT) has been associated with a subpopulation of tumor cells with stem cell like features like self-renewal and pluripotency, which are referred to as CSCs. EMT has been postulated as a mechanism facilitating their invasiveness. However, there are data questioning the relevance of this mechanism for cancer stem cells (Tiran et al., 2017). Results showed an upregulation of CD26 in metastatic breast cancer cells and, most noteworthy, an upregulation of CD26 in the in vitro model for malignant transformation, which was further increased in the cell line modeling EMT. These findings are in line with previous studies that associated CD26 with invasiveness in some cancers (Donnenberg et al., 2018). Tumor necrosis factor alpha (TNF-α) upregulation has been reported in breast cancer and enables cancer cell survival, proliferation, angiogenesis and invasion (Miles et al., 1994; Waters, Pober, & Bradley, 2013). One study was able to show that TNF-α increases CD26/DPP4 expression in vitro (Wolczyk et al., 2016). Correspondingly, Choi et al. identified a potential mechanism of CD26/DPP4-induced epithelial transformation in breast cancer. Peptidylprolyl cis/trans isomerase, PIN1, is a target gene of the transcription factor E2F1, which is upregulated in breast cancer and correlates with tumor grade and cell cycle progression. In vitro data from human breast cancer cells (MCF7) revealed that CD26/DPP4 increased PIN1 expression by activating the transcription factor E2F1 via epidermal growth factor, strongly suggesting CD26 as a potential therapeutic target in primary human breast cancer (Choi et al., 2015).

The interaction of CSC with the tumor microenvironment has been previously reported and enables these cells to escape systemic therapy. Human breast stromal fibroblasts were sorted according to their expression levels of CD26 and CD105, a type I membrane glycoprotein belonging to the Transforming Growth Factor-ß receptor complex that is expressed on fibroblasts and linked to angiogenesis and tumorigenesis. Thereby, two distinct fibroblast groups were distinguished, lobular fibroblasts ($CD105^{high}/CD26^{low}$) and interlobular fibroblasts ($CD105^{low}/CD26^{high}$). Among these distinct fibroblast lineages, the lobular fibroblasts with low CD26 expression were able to differentiate into adipogenic and osteogenic cell lines, thus portraying properties of mesenchymal stem cells which support development of epithelial cells. Additionally, these stem cell-like fibroblasts might provide the microenvironment for human breast luminal epithelial

progenitor cells, which can develop into breast cancer cells in malignant transformation (Morsing et al., 2016). The development of epithelial organs are known to require epithelial-mesenchymal interactions (Ball & Risbridger, 2001; Morsing et al., 2016). The reason for these fibroblasts with stem cell features to exhibit low CD26 expression might be due to the characteristics of these cells, residing in the periductal environment, differentiating into various stromal cells without requiring invading capability, which has been linked to high CD26 expression.

CD26 is heterogeneously expressed in breast cancer with in vitro data indicating differences in expression among the different histological subtypes (Leccia et al., 2012). Moreover, CD26 was found to induce epithelial transformation in breast cancer by increasing PIN1 expression (Choi et al., 2015). Interestingly, a certain type of fibroblasts were identified as CSCs in breast cancer that only showed low CD26 expression, which might be due to their low invading capability (Morsing et al., 2016). All in all, these findings portray CD26 as a potential prognostic marker and as a therapeutic target.

2.7.2. Ovarian cancer

An immunohistochemical study investigating the expression of CD26 in 199 epithelial ovarian cancer samples showed a CD26 expression in 82.8% of samples and was significantly higher compared to borderline ovarian cancer or benign ovarian tumors. In situ mRNA hybridization revealed CD26/DPP4 expression at mRNA level in 97.7% of ovarian cancer samples (Zhang, Xu, et al., 2015) corroborating a previous study in 378 epithelial ovarian carcinoma's (Zhang, Qiao, & Suo, 2008). In vitro studies have linked CD26 expression in ovarian cancer cell lines to low invasive potential and vice versa. Moreover, CD26 was associated with increased adhesion, binding to collagen and fibronectin. In vivo, CD26-transfected cells showed longer survival than control cells (Kajiyama et al., 2003, 2002; Kikkawa et al., 2005). Kajiyama and colleagues investigated the role of CD26/DPP4 in paclitaxel resistance of epithelial ovarian cancer. In vitro data from these cell lines revealed a positive correlation of DPP4 expression and paclitaxel sensitivity which significantly increased with DPP4 overexpression and did not change under DPP4 inhibition. In vivo, using a subcutaneous mouse model treated with paclitaxel, the tumor size that consisted of DPP4-transfected cells was smaller compared to the tumor of vector-inoculated cells. These results show that CD26 might increase chemotherapy sensitivity for paclitaxel independently of its enzymatic activity (Kajiyama et al., 2010).

Evaluating the prognostic value of CD26/DPP4 in ovarian cancer, CD26/DPP4 expression correlated with lymph node metastasis and clinical stage of the disease. In contrast, there was no significant correlation found with histological grade, tumor type or disease free survival (Zhang, Xu, et al., 2015). Especially the correlation with the occurrence of lymph node metastasis might prove valuable as a predictive marker. In contrast, in a study with a larger patient cohort and focusing on one histological entity, a positive correlation with histological type and shorter overall free survival was found (Zhang et al., 2008). This leads to the quest for a further evaluation of CD26 as a prognostic biomarker with larger patient numbers and analyzing for the histological types.

CD26 is overexpressed in most ovarian cancer samples (Zhang et al., 2008, Zhang, Xu, et al., 2015). CD26 expression was linked to low invasive capability and increased adhesion to ECM in vitro and longer cell survival in vitro (Kajiyama et al., 2003, 2002; Kikkawa et al., 2005). Moreover, CD26 showed prognostic relevance, positively correlating with chemotherapy-sensitivity (Kajiyama et al., 2010), lymph node metastasis and clinical disease stage (Zhang, Xu, et al., 2015) as well as histological type and shorter overall free survival (Zhang et al., 2008).

2.7.3. Endometrial cancer

Research on CD26/DPP4 expression in endometrial cancer is quite limited to date. CD26/DPP4 is expressed in healthy glandular cells of the endometrium, albeit, was found to be downregulated in endometrial adenocarcinoma with increasing tumor grade. In parallel, *regulated on activation, normal T cell expressed and secreted* (RANTES), a substrate of CD26/DPP4, was overexpressed in endometrial carcinoma and increased proliferation of endometrial adenocarcinoma cell lines HEC-1-A and Ishikawa in vitro (Khin et al., 2003). These findings could indicate a possible anti-oncogenic effect of CD26/DPP4 in endometrial cancer by degrading substrates such as RANTES. In support of this, Mizokami et al. demonstrated that the DPP4 substrate CXCL12 and its receptor CXCR4 are expressed in endometrial cancer. CXCL12 stimulated cell proliferation in vector-transfected cells, however, had no effect on CD26/DPP4-transfected cells, suggesting a regulating effect of CD26/DPP4 on tumor growth in endometrial cancer (Mizokami et al., 2004).

However, a recent study revealed contradictory results: CD26/DPP4 overexpression induced cell proliferation, invasion and tumorigenesis in vitro in endometrial cancer cell lines Ishikawa, HEC-1-B and AN3-CA and in vivo by injecting CD26/DPP4-transfected AN3-CA cells into nude mice. CD26/DPP4 knockdown and DPP4 inhibition with sitagliptin prohibited these effects, indicating the relevance of DPP4 inhibitors in therapy of endometrial cancer (Yang et al., 2017). On the one hand, these seemingly opposing results might be due to the changes in CD26/DPP4 expression depending on tumor stage, in which case the relevant effect of CD26/DPP4 in the respective stage of tumorigenesis is still to be determined. On the other hand, the multifunctional character of the CD26/DPP4 molecule with its various substrates enables contrasting effects. Consequently, these important, yet differing in vitro and in vivo results might be due to methodological differences, depending on the characteristics of the employed cancer cell line or the substrate investigated. The clinical relevance of these CD26/DPP4 substrates is not fully understood yet.

2.7.4. Cervical cancer

Cervical cancer is the second most common gynecological malignancy after breast cancer with histopathological subtypes SCC and adenocarcinoma. One in vitro study has investigated CD26 expression and activity in cervical cancer cell lines so far, reporting the highest CD26/DPP4 expression in the cancer cell line SiHa and in the immortalized epithelial cell line HaCaT, whereas the expression was low in C33A cells and barely expressed in HeLa cells (Beckenkamp et al., 2015). DPP4 activity was detected in all cell lines with the highest activity level in SiHa cells. The inhibition of DPP4 activity with sitagliptin increased cell migration in the SiHa cell line and reduced adhesion in culture. However, DPP4 inhibition also reduced adhesion in HeLa cells, which scarcely expressed CD26/DPP4 and showed greater migratory behavior compared to SiHa cells. The authors concluded that cell adhesion might be regulated independently from DPP4 activity. It has been shown that DPP8/9 is expressed in HeLa cells while DPP4 is not (Wilson & Abbott, 2012). However, it remains unclear whether the low DPP4 activity measured in HeLa cells is attributable to DPP4 or rather DPP8/9. Since it is known that CD26/DPP4 is associated with increased adhesion and reduced migratory behavior in some cancers, such as ovarian cancer, these findings suggest a similar role of CD26/DPP4 in cervical cancer. Due to this, the authors surmised that the sitagliptin-induced reduction of adhesion in barely CD26/DPP4-expressing HeLa cells might be due to an off-target effect of sitagliptin. A study in patients with T2DM revealed decreased plasma levels of the cell adhesion molecules endothelial selectin and, in some cases, intercellular adhesion molecule 1 after sitagliptin treatment (Tremblay, Lamarche, Deacon, Weisnagel, & Couture, 2014). Although this effect is probably caused by glucagon-like peptide 1-inhibition thus inhibiting endothelial activation with increased expression of cell adhesion molecules, it illustrates the potentially plural effects that might follow treatment with this substance. Further studies using CD26/DPP4-knockdown animal models or with human cervical cancer specimens are recommended.

Thus far, CD26 expression has only been investigated in cervical cancer cell lines (Beckenkamp et al., 2015), but not in clinical tumor samples. Moreover, the exact role of CD26/DPP4 and the related enzymes DPP8/9 in cervical cancer still remains unclear (Wilson & Abbott, 2012).

2.8. Gastrointestinal malignancies

2.8.1. Colorectal cancer

CD26/DPP4 is not expressed in normal colon epithelium but has been found to be variably expressed in colon cancer, as discussed in a previous review (Havre et al., 2008). CD26/DPP4 expression is increased during enterocyte differentiation in colon adenocarcinoma cell lines Caco-2 and HT-29 and thus functions as a marker for intestinal epithelial differentiation (Darmoul et al., 1992; Ducarouge et al., 2017). Interestingly, CD26/DPP4 expression and activity were linked to the confluence of the Caco-2 cells (Pandrea et al., 2000). However, the substrate used is not specific for DPP4, and shortly after this publication, DPP8 and DPP9 were discovered (Abbott et al., 2000; Olsen & Wagtmann, 2002), making it possible that the reported activity is not fully related to CD26/DPP4. Abe et al. further investigated the mechanism involved in confluence-dependent changes in CD26/DPP4 expression in vitro. Colon adenocarcinoma cells HCT-116 and HCT-15 were cultured until confluence and presented an increased CD26 expression at protein and mRNA level. c-MYC, a proto-oncogene involved in cell proliferation and cell cycle progress in cancer (Vita & Henriksson, 2006), was decreased in confluent cells and inhibited CD26/DPP4 expression upon c-Myc-transfection of cells, functioning as a repressor of CD26/DPP4 expression. In contrast, caudal type homeobox 2, a homeobox-protein involved in regulating intestinal cell differentiation (Silberg, Swain, Suh, & Traber, 2000), was increased upon confluence in the cell line HCT-15 and induced CD26/DPP4 expression (Abe et al., 2011). These findings determine potential transcriptional regulators of CD26/DPP4 expression in confluent colon carcinoma cells and might provide a therapeutic target. However, some data indicate that other factors, like serum depletion (Abe et al., 2011) might contribute to increased CD26/DPP4 expression as well.

Apart from this, current research has focused on CSCs in CRC. Cancer stem cell markers detected so far include $CD133^+$, highly expressed epithelial cell adhesion molecule, $CD166^+$ and $CD44^+$, however, no marker by itself was able to reliably distinguish CRC stem cells from regular cancer cells (Gemei, Di Noto, Mirabelli, & Del Vecchio, 2013). In this context, CD26/DPP4 was investigated to identify and further characterize this unique subpopulation of colon cancer cells. CD26 expression was found inconsistently in colon cancer cell lines representing different differentiation stages, being positive in cell lines HT29, HCT116 and Caco-2, yet negative in the more differentiated GEO cell line (Gemei et al., 2013). These results are in favor of CD26 as a marker for a subset of cancer stem cells. Indeed, Pang et al. established $CD26^+$ CSCs as a subpopulation of CSCs that are present in both the primary tumor and metastases of patients with metastasized CRC. CD26-expressing cells showed increased invasive behavior and chemoresistance. Furthermore, the presence of $CD26^+$ cells in CRC was found to be a predictor for the occurrence of metastasis, which could facilitate stratification for adjuvant therapy (Pang et al., 2010). However, CD26-knock-down in $CD133^+$ cells did not increase chemotherapy sensitivity, proposing other mechanisms involved in the development of chemotherapy-resistance (Grunt et al., 2015). The Notch signaling pathway plays an important role in carcinogenesis and is a prominent signaling pathway in chemotherapy resistant cancer (Wang et al., 2010). Notch-2, one of four different receptors, showed the highest expression in colon CSCs (CelProgen; E36112-39P) and knock-down of Notch-2 and -3 led to a decreased CD26/DPP4 expression (Apostolou et al., 2013). Interestingly, CSC markers were decreased under suppression of Notch-2 (Apostolou et al., 2013), introducing the Notch receptors, especially Notch-2 as a potential member involved in chemotherapy resistance of colorectal CSCs. Another study investigated if acquired chemotherapy resistance was linked to stemness. Analysis for cancer stem cell markers and EMT markers in CSCs derived from two different cancer cell lines, HT29 and HCT116, revealed some shared phenotypic traits such as increased expression of CD26, CD166 and Multiple Drug Resistance 1 (MDR1) genes (El Khoury, Corcos, Durand, Simon, & Le Jossic-Corcos, 2016).

In colorectal cancer, CD26/DPP4 was identified as a potential marker for enterocyte differentiation in colon adenocarcinoma cell lines (Darmoul et al., 1992; Ducarouge et al., 2017; Pandrea et al., 2000). Interestingly, CD26 was also found to be a marker for $CD26^+$ CSCs, a subpopulation of CSCs present in both the primary tumor and metastases showing increased invasion and chemoresistance (Pang et al., 2010). However, the mechanisms contributing to chemotherapy resistance are not fully understood yet, since a CD26-knock-down in $CD133^+$ cells did not increase chemotherapy sensitivity (Grunt et al., 2015).

2.8.2. Gastric cancer

Although there are currently limited data on CD26/DPP4 expression in gastric cancer (Carl-McGrath et al., 2004), it has gained relevance as a distinct marker for gastric CSCs (Nishikawa et al., 2015). In this study, CSCs were isolated from clinical gastric cancer samples and their expression profile was characterized with a surface marker antibody-array, flow cytometry and an in vivo model. Subpopulations of gastric CSCs with distinct tumorigenicity were identified based on the markers CD44 and CD26. $CD26^+/CD44^+$ cells showed the highest tumor-forming capacity and $CD26^-/CD44^-$ CSCs revealed very low to absent tumorigenesis in vivo. Another study confirmed CD26 as a marker for the invasive phenotype of gastric CSCs and identified IL-17 as the mechanism by which 'quiescent', $CD26^-/CXCR4^-$ gastric CSCs are transformed into a more invasive phenotype (Jiang et al., 2017). In vitro and in vivo, IL-17 treated cells displayed an increased invasion, migration and tumorigenesis. These findings suggest that CD26 and IL-17 are involved in the formation of the CSC phenotype, thus qualifying as a therapeutic target in gastric cancer, potentially increasing chemotherapy susceptibility and reducing tumor progression. However, more data on the expression of CD26/DPP4 in gastric cancer are needed in order to make a more robust statement.

2.9. Esophageal cancer

Immunohistochemical staining for CD26 was positive in dysplastic squamous epithelial and esophageal squamous cancer cells (Goscinski, Suo, Nesland, Chen, et al., 2008). Moreover, a higher expression was detected in SCC cell lines than in non-tumor esophageal epithelial cells. Overexpression of CD26 in SCC was also confirmed via reverse transcription polymerase chain reaction in another study (Augoff et al., 2014). Comparison of CD26 expression in SCC with adenocarcinoma of the esophagus showed a significantly higher expression in adenocarcinoma (Goscinski, Suo, Nesland, Flørenes, and Giercksky, 2008). Overexpression in adenocarcinoma cells was even linked to distant metastasis in patients. Comparison of CD26 expression in stromal cells of the different histological entities, however, revealed a significantly higher expression in SCC stroma compared to stromal cells of adenocarcinoma. Interestingly, a high CD26 expression level correlated with longer survival in SCC patients ($n=144$) (Goscinski, Suo, Nesland, Chen, et al., 2008), although there was no correlation found in another study ($n=90$) of the same research group (Goscinski, Suo, Nesland, Flørenes, et al., 2008). In adenocarcinoma tissue samples ($n = 69$) there was no correlation found with survival, either (Goscinski, Suo, Nesland, Flørenes, et al., 2008). In light of the association with distant metastasis, CD26 overexpression in esophageal adenocarcinoma might have a different prognostic impact than in SCC, which still needs to be examined. Of note, soluble CD26 is a relevant prognostic factor in esophageal SCC which will be discussed below in more detail (Xinhua, Xiangting, Lingling, & Guohong, 2016). A recent publication introduced an elegant method to utilize CD26 tissue expression for early endoscopic detection of esophageal SCC (Onoyama et al., 2016). DPP4-activated fluorescent substances were able to identify tumor tissue in endoscopic and surgical specimens. In biopsy samples, most importantly, this method reached a sensitivity of 96.9% and specificity of 85.9%. These results are comparable to another method, lugol endoscopy, which has reportedly caused side effects and poses diagnostic difficulties due to variable staining. One noteworthy benefit of making use of CD26/DPP4 surface expression

is the possibility for using it topically in situ as well as on biopsy material, rather than requiring intravenous application along with its safety concerns (Onoyama et al., 2016). Perhaps, to increase specificity, a combined approach staining for multiple cell surface markers might be successful, such as FAP, matrix metalloproteinase (MMP)-2, -9 and membrane-type metalloproteinase 1 which have been reported in esophageal SCC as well (Augoff et al., 2014).

To conclude, CD26 is overexpressed in both SCC and adenocarcinoma of the esophagus, however, with a significantly higher expression in esophageal adenocarcinoma in comparison to SCC. Interestingly, there was a significantly higher stromal CD26 expression in SCC than in adenocarcinoma (Goscinski, Suo, Nesland, Flørenes, et al., 2008). High CD26 expression correlated with longer survival in SCC patients (Goscinski, Suo, Nesland, Chen, et al., 2008), however, overexpression was associated with distant metastasis in adenocarcinoma (Goscinski, Suo, Nesland, Flørenes, et al., 2008). According to these findings, CD26 expression might play a different prognostic role in each histological subtype of esophageal cancer. Additionally, CD26 expression is utilized to detect tumor tissue endoscopically and in surgical specimens (Onoyama et al., 2016).

2.10. Hepatocellular carcinoma

CD26 expression was determined in tumor specimens of hepatocellular carcinoma (HCC) and in cancer cell lines HepG2 and Huh7 (Kawaguchi et al., 2015). CD26 mRNA from HCC tissue was significantly increased and high CD26 expression levels were associated with a significantly larger tumor size, thus possibly inducing tumor growth. HCC cell lines analyzed with flow cytometry showed high CD26 expression. CD26 knockdown with siRNA in vitro led to suppression of tumor growth through cell cycle arrest in both cancer cell lines. Nishina et al. analyzed immunohistological stainings of HCC specimens with varying grades of CD26 expression (Nishina et al., 2019). Interestingly, a high grade of CD26 expression was associated with factors such as a higher tumor stage, less differentiated tumors and a higher proliferation marker Ki-67, however, these findings were not significant. Moreover, the figure provided by the authors indicates that $CD26^+$ TILs might have been graded as a low grade of CD26 expression, not the tumor cells alone. Accompanying increased CD26 expression, the serine protease inhibitor SerpinB3 was found to be upregulated in HCC as well (Fasolato et al., 2018). Both markers displayed a similar localization pattern in the tumor and correlated with tumor differentiation grade. In SerpinB3-transfected HCC cells, CD26/DPP4 was upregulated, representing a possible compensatory feedback mechanism upon SerpinB3-mediated inhibition of DPP4 enzymatic activity (Fasolato et al., 2018). Another recent study investigated the role of DPP4 in HCC induced by a high-fat diet (HFD) (Qin et al., 2018). Obesity has been previously reported as a major risk factor for HCC and it has been associated with increased serum DPP4 levels (Bostick et al., 2014; Larsson & Wolk, 2007). In a N-nitrosodiethylamine induced HCC model in rats, a HFD was linked to an elevated DPP4 activity and increased occurrence of HCC, tumor size and the occurrence of lung metastases (Qin et al., 2018), which will be further discussed in the section on therapy.

All in all, CD26 plays a pro-oncogenic role in HCC and thus serves as a potential therapeutic target and negative prognostic marker.

2.11. Renal cell carcinoma

CD26/DPP4 expression is found on healthy epithelial cells of the proximal tubulus (Varona et al., 2010) as well as on renal carcinoma cells (Kehlen, Göhring, Langner, & Riemann, 1998) and in different cancer cell lines (Havre et al., 2008; Inamoto et al., 2006). Varona et al. characterized CD26/DPP4 activity, protein and mRNA expression in human tissue samples of clear cell renal carcinoma, chromophobe renal cell carcinoma, and renal oncocytoma. Analysis of membrane-bound DPP4 activity revealed a significant downregulation of DPP4 in all tumor subtypes. Moreover, cytoplasmic DPP4-like activity correlated positively with higher tumor grade of clear cell renal carcinoma as a marker for aggressiveness (Varona et al., 2010). In support of this, higher cytoplasmic DPP4-like activity in tissue samples from clear cell carcinoma patients was linked with a significantly shorter five-year survival rate (Larrinaga et al., 2012). However, it is possible that the measured cytoplasmic DPP4-like activity is in fact the sum of DPP4- and DPP8/9 activity. In contrast to these findings, the Human Protein Atlas lists DPP4 as a favorable prognostic marker in renal cell carcinoma (The Human Protein Atlas, 2018a).

2.12. Prostate cancer

Previous studies have demonstrated an increase of DPP4 activity in prostate cancer as well as in the transformation zone in comparison to the peripheral zone or normal prostate tissue (Wilson et al., 2005, 2000). However, the measurement conditions do not preclude interference by DPP8/9, thus there is the possibility that DPP4-like enzymatic activity caused by these enzymes was measured as well. Immunohistochemical analysis of prostate cancer specimens showed that CD26 was overexpressed in prostate cancer tissue in comparison to normal tissue (Lu et al., 2013). However, a previous study reported a downregulation during malignant transformation or tumor progression as well as a potential anti-oncogenic effect of CD26/DPP4 in vitro (Wesley, McGroarty, & Homoyouni, 2005). Moreover, there is evidence for a downregulation of CD26/DPP4 expression in metastases compared to primary prostate cancer tissue (Bogenrieder et al., 1997; Dinjens et al., 1990). In support of this, CXCL12 and its receptors CXCR4 and CXCR7 seem to be relevant for metastasis of prostate cancer (Sun et al., 2003; Taichman et al., 2002; Wang et al., 2008). An in vitro study of the same research group in prostate cancer cell lines demonstrated that CD26/DPP4 was the responsible protease for degrading CXCL12 and confirmed in vivo that CD26/DPP4 inhibition facilitated metastasis (Sun et al., 2008).

In a prostate cancer murine xenograft model with VCaP, a human prostate cancer cell line, Russo et al. identified DPP4 as an androgen receptor-stimulated tumor suppressor gene that is downregulated when the cancer progresses to castration-resistant prostate cancer. Downregulation of DPP4 was mediated epigenetically, shown by an increased DPP4 protein level after intraperitoneal testosterone applications. Correspondingly, DPP4 inhibition with sitagliptin encouraged progress despite castration in different xenograft models. Also in clinical samples of castration-resistant prostate cancer a decrease in DPP4 protein was found (Russo et al., 2018). In contrast, others reported that CD26 correlated with PSA level, tumor residue, cancer stage and tumor size (Lu et al., 2013). Additionally, the Human Protein Atlas reported DPP4 as an unfavorable prognostic marker for prostate cancer (The Human Protein Atlas, 2018a).

While in vitro and in vivo results suggest that CD26 is a tumor suppressor in prostate cancer (Russo et al., 2018; Wesley et al., 2005), CD26 expression is also correlated with PSA level and cancer stage, suggesting that it is a negative prognostic marker (Lu et al., 2013). Considering these contradictory findings, the role of CD26/DPP4 in prostate carcinoma needs to be further investigated regarding potential different functions of CD26/DPP4 in different tumor stages and in metastatic disease. However, as the number of cases in the study examining the correlation of CD26 expression with clinical parameters was limited ($n = 36$), a larger patient cohort is needed to establish whether CD26 is indeed an effective prognostic marker.

2.13. Other tumor entities

CD26 expression was shown to be significantly higher in osteosarcoma than in normal bone tissue (Zhang, Lin, Mo, Chen, & Lin, 2013). Moreover, analysis of 116 patients revealed CD26 expression as an independent negative prognostic factor for overall and disease-free survival.

However, co-expression of CD26 and CD10 proved to be the strongest prognostic predictors in this regard (Zhang et al., 2013).

One study with a small number of patients reported CD26/DPP4 expression (alongside FAP) in certain soft tissue tumors (Dohi et al., 2009). However, due to the limited study size these results would need confirmation in a larger study setting.

Liang et al. showed that CD26/DPP4 is highly expressed in invasive high-grade urothelial cell carcinoma, with high CD26/DPP4 expression being significantly correlated to higher tumor stage, occurrence of nodal metastases, vascular and perineural invasion (Liang et al., 2016). The prognostic role of CD26/DPP4 expression in urothelial cell cancer is discussed below.

DPP4 expression was also found in pancreatic ductal adenocarcinoma (n = 93) in 95% of tumors and in addition, to a lower degree, in stromal cells of peritumoral tissue (Busek et al., 2016). This article will be discussed in more detail in the section on soluble CD26.

To conclude, due to its varying biological role in tumorigenesis depending on the tumor entity and the potential ligands examined, CD26 expression was found to be either up- or downregulated in the respective cancer tissues. While mostly acting as a pro-oncogene, in some tumors it displays an anti-oncogenic function, which was, for instance, linked with the CXCL12-axis in glioma and prostate cancer. The studies discussed above have revealed findings relevant for a better understanding of the role of CD26 in cancer development. Aside from providing new evidence on CD26/DPP4 expression in cancers with limited or no data on this area of research so far, different mechanisms involved in the CD26-mediated effects in cancer were identified. This includes the CXCL12-axis, which is known to increase cell migration and invasion and illustrates the potential plurality of CD26-induced effects in cancer. For instance, while CD26 degraded CXCL12 in glioma and prostate cancer tissue, it was reported to increase CXCL12 on T cell lines, enhancing their invasive capability. Most importantly, the influence of the experimental setting, the biological material examined as well as the limitations of transferring in vitro results to tumor biology in vivo and the human biological system need to be taken into consideration when interpreting and comparing research on CD26/DPP4 expression in tumors. For instance, DPP4 enzymatic activity expressed in tumor tissue is determined less frequently than in plasma or serum of cancer patients. Indeed, the possibility of enzymatic activity of related enzymes interfering with the measured CD26/DPP4 activity needs to be taken into consideration. Moreover, across studies the term soluble CD26 is used inconsistently, for the secreted CD26 as well as solubilized CD26 from tissue lysate. Current studies have provided valuable new insights into CD26/DPP4 expression in cancer, the underlying mechanisms of the anti- or pro-oncogenic effect and its role as a cancer biomarker. Consequently, there is a need for follow-up studies on this new evidence to fully understand the individual role of CD26 in different tumor entities. One area of interest might be the recently detected prognostic value of stromal CD26 expression in rectal cancer, which might prove relevant in other cancers as well. Furthermore, our own unpublished data on CD26 expression in human lung cancer tissue show different expressional patterns across histological subtypes, hence qualifying CD26 as a potential biomarker and therapeutic target in human NSCLC.

3. The role of CD26/DPP4 in the development of metastases

The presence of metastases confirms the systemic nature of a malignant disease and remains the primary cause of cancer death. The pathways that lead to the spread of tumor cells are complex and not completely understood. However, some key mechanisms of how cancer cells escape from the primary tumor, how they enter the blood stream and extravasate to form new tumor colonies in secondary organs are discussed by numerous studies. These mechanisms require the action of a wide variety of cytokines, chemokines, ligands, receptors and other molecules. In this context, the transmembrane receptor CD26 is ascribed a pivotal role in malignant cell invasion and metastasis. The experimental development of metastases in different CD26 mutant rat strains (Shingu et al., 2003), the clinical development of lymph node metastases in ovarian cancer (Zhang, Xu, et al., 2015) and also the observation that CD26 expression levels in the tumor were significantly higher in CRC patients bearing distant metastasis than in non-metastatic tumors, all point to an involvement of CD26/DPP4 in invasion and metastasis (Hirai, Kotani, Aratake, Ohtaki, & Kuma, 1999; Lam et al., 2014).

3.1. Mechanistic role of CD26 in the development of metastases

Early experimental work from Pauli and colleagues showed that besides the enzymatic and T cell activating properties of CD26, lung endothelial CD26 binds to extracellular proteins such as collagen and fibronectin. Breast tumor cells are known to capture a large amount of polymeric fibronectin, the natural ligand of CD26 and therefore CD26 mediates the adhesion of lung metastatic breast cancer cells, leading to lung vascular arrest and formation of lung metastasis (Cheng et al., 2003; Cheng, Abdel-Ghany, Elble, & Pauli, 1998). This study showed that adhesion of the cancer cells on the endothelium was abolished upon inhibition of CD26 by the monoclonal antibody (mAb) 6A3. The same group also showed that the interaction between a truncated DPP4 variant and fibronectin was effective in controlling tumor cell colonization in an experimental animal model (Abdel-Ghany, Cheng, Levine, & Pauli, 1998). However, when employing a mutant DPP4 expressed by lung capillary endothelia, even if this mutant DPP4 was greatly diminished in Fischer 344/CRJ rats, it was sufficient to cause arrest of a large number of breast cancer cells in the lung vasculature and to promote the generation of lung colonies (H. C. Cheng, Abdel-Ghany, Zhang, & Pauli, 1999) supporting the notion that several, often parallel mechanisms involving multiple tumor and host factors, mediate metastatic spread of cancer cells. A similar mechanism could be shown in human esophageal squamous cell carcinoma in which the expression of DPP4 could be correlated with an increased degradation of the extracellular matrix, thus facilitating cancer cell invasion and metastasis (Augoff et al., 2014).

The peptidase activity of CD26/DPP4 cleaving N-terminal dipeptides from polypeptides with either L-proline or L-alanine at the penultimate position, allows the cleavage of a number of chemokines and other peptides which are involved in cell regulation, migration and the invasion of metastases. For example, CXCL12, a strong chemoattractant of stem cells (Anderluh et al., 2016), and macrophage-derived chemokine (CCL22) both induce leucocyte migration and are natural substrates of DPP4 (Lambeir et al., 2001). CXCL12 binds to the widely expressed CXCR4 and regulates key aspects of development, stem cell motility and tumor metastasis to tissues with high levels of CXCL12. In this context, it has been shown that the removal by DPP4 of the two N-terminal amino acids from CXCL12 resulted in significantly reduced chemotactic and calcium-signaling activity due to a decreased affinity for CXCR4 (Proost et al., 1998; Shioda et al., 1998). The metastatic process is functionally similar to the migrational or 'homing' behavior of hematopoietic stem cells to the bone marrow wherein CXCL12 and its receptor CXCR4 are key elements. Sun and colleagues found in a prostate cancer mouse model that when inhibiting CD26/DPP4, invasion and metastasis of prostate cancer cell lines were enhanced in both in vitro and in vivo metastasis assays. This suggests that the degradation of CXCL12 by CD26/DPP4 may be involved in the metastatic cascades of prostate cancer. Moreover, it suggests that inhibition of CD26/DPP4 may be a trigger of metastasis (Sun et al., 2008). These findings are corroborated by data from Narducci and colleagues who suggest that in Sézary syndrome, a cutaneous T cell lymphoma, cellular recruitment and homing to tissues and in the metastatic process depends on the CXCL12-CXCR4 axis through the regulatory activity of CD26 (Narducci et al., 2006). Further evidence that CXCL12 promotes the development of metastases comes from Lefort and Blay. They investigated the effect of the flavonoid apigenin, known for its beneficial effects on cancer, and they found that apigenin enhances cell-surface levels of CD26/DPP4 on CRC cell lines. The observed cellular actions may suggest an anti-

metastatic potential for apigenin (Lefort & Blay, 2011). A very recent study confirmed the beneficial action of apigenin in NSCLC cells with different epidermal growth factor receptor status (Chang et al., 2018). The mechanism involved suppression of p-Akt and Snail/Slug signaling and the EMT-mediated invasive ability. Here, apigenin downregulated CD26/DPP4 expression in all tested NSCLC cells. The authors also showed an anti-metastatic effect of apigenin and a metastasis-promoting effect of CD26 in a human A549 xenograft model. Finally, in a dataset of more than 800 lung cancer patients, a significantly shorter time-to-recurrence was observed for CD26-^{high}/Akt^{high} compared to CD26^{low}/Akt^{low} patients (Chang et al., 2018). It remains to be elucidated whether the change in CD26 expression is functionally related to the beneficial effect of apigenin in cancer or is just an epiphenomenon.

In pancreatic cancer, it was found in both in vitro and in vivo experiments that the expression of CD26 was higher in cell lines derived from metastases than those from the primary tumor sites (Ye, Tian, Yue, et al., 2016). Furthermore, knockdown of CD26/DPP4 expression inhibited the growth of cells, migration, invasion, colony formation, and increased cell apoptosis of pancreatic cancer cells and also decreased the development of liver metastasis in a xenograft animal model. Our own group found an anti-tumor effect of vildagliptin on colorectal lung metastases via downregulation of autophagy resulting in increased apoptosis and modulation of the cell cycle (Jang et al., 2015). On the other hand, DPP4 has been assigned a tumor suppressor function, at least in an in vitro study of a metastatic prostate cancer (Wesley et al., 2005). Wesley and colleagues showed in metastatic prostate cancer that the loss of CD26/DPP4 is associated with increased production of basic fibroblast growth factor, a powerful mitogen, concluding that DPP4 inhibits the malignant phenotype of prostate cancer cells by blocking basic fibroblast growth factor signaling (Wesley et al., 2005).

3.2. Subpopulation of CD26$^+$ stem cells during the development of metastases

CD26 is present on a subpopulation of stem cells that is involved in cancer genesis and promotion. Several studies have focused on this subpopulation, mainly on experimental colon cancer models but also in gastric cancer models in vitro and in vivo (Bleau, Agliano, Larzabal, de Aberasturi, & Calvo, 2014; Liao, Ye, Deng, Bian, & Ding, 2014; Nishikawa et al., 2015). CSCs not only promote primary tumor growth, but also initiate metastases formation. Pang and colleagues identified a subpopulation of CSCs from human tumors that are capable of forming metastasis in an orthotopic mouse tumor model. They isolated the subpopulation of CD26$^+$ CSCs from metastatic colorectal tumors in the liver and demonstrated that CD26$^+$ CSCs isolated from primary tumors were equally capable of forming metastasis. Moreover, they showed that the presence of CD26$^+$ colorectal CSCs in the primary tumor was predictive of development of metastasis on clinical follow-up (Pang et al., 2010). Recent work from Cheung and colleagues revealed a subpopulation of CD26$^+$ colorectal CSCs to be implicated in metastasis (Cheung et al., 2017). Although the study suffers from a low number of samples, the authors hypothesize that this subpopulation of CSCs arises in the late stage of carcinogenesis from the bulk of tumor daughter cells which are CD26$^-$. There is substantial clinical evidence that tumor cells resistant to chemotherapy represent an aggressive subpopulation of cells that could lead to metastatic dissemination and relapse of the disease. CD26$^+$ CSC have been identified as cancer-initiating cells that survive exposure to chemotherapy and as markers of long-term growth and resistance in the HCT-116 colon cancer cell line (Durinikova et al., 2018; Grunt et al., 2015). The fact that soluble CD26 in postoperative serum can serve as a marker for disease recurrence even before the metastases were diagnosed, additionally underscores the relevance of this molecule in the follow-up of colon cancer (see also paragraph on sCD26) (De Chiara et al., 2014).

3.3. CD26/DPP4 inhibition and the risk of metastases in patients

Since many years, CD26/DPP4 inhibitors have been used worldwide as anti-diabetic drugs with a safe profile. Taking into account the above described mechanisms that potentially decrease the risk of metastases development, the question arises if an association between this type of glucose-lowering treatment and new-onset metastatic cancer among T2DM patients with comorbid incident cancer exists. In this context, Rathman and Kostev analyzed, in an observational study, the relationship between prescription use of DPP4 inhibitors and the risk of the development of metastases in T2DM patients suffering from breast, prostate, or intestinal organ cancers. They found that DPP4 inhibition was not associated with a higher risk of metastases within three to four years after cancer diagnoses (Rathmann & Kostev, 2017). In a very recent study, Noh et al analyzed a cohort of 223.530 diabetic patients newly diagnosed with primary cancer (Noh, Jeon, & Shin, 2018). They received a DPP4 inhibitor either alone or in combination with metformin. DPP4 inhibitor therapy was not associated with a significant risk of cancer metastasis relative to no anti-diabetic therapy, irrespective of patient age and sex, except for thyroid cancer (Noh et al., 2018).

Others recently found opposing effects of this anti-diabetic treatment in cancer patients: the DPP4 inhibitors saxagliptin and sitagliptin did not increase tumor incidence but increased the risk of metastasis of existing tumors. The induction of a prolonged activation of the nuclear factor E2-related factor 2 is proposed as a mechanism (Wang et al., 2016). In a xenograft mouse model, DPP4 inhibitors resulted in an upregulated expression of metastasis-associated proteins, increased cancer cell migration, and promotion of metastasis. Summarizing these data, which are scarce to date, there is no clear evidence that DPP4 inhibitors protect against or promote metastases. To answer this question, clinical multicenter studies with a long follow-up period are required.

Though the evidence with regard to the development of metastases is scarce for the DPP4 related enzymes DPP8 and DPP9, it was clearly shown that DPP9 gene silencing and treatment with a DPP8/DPP9 specific inhibitor both reduced cell adhesion and migration (Zhang, Chen, et al., 2015) and emphasizes the relevance of also these proteases in tissue and tumor growth and metastasis.

4. The importance of CD26$^+$ tumor infiltrating lymphocytes (TILs)

The previous section considered CD26 expression by tumor cells themselves. CD26 is a well-established marker for a number of leukocyte subsets (reviewed by Waumans et al., 2015). In lymphocytes, different subsets of CD4 and CD8 T cells can be distinguished according to their level of CD26 expression. The characterization as CD26^{neg}, CD26^{int} and CD26^{high} lymphocyte subsets reveals distinct features that are important for the anti-cancer immune response. Recent work by Bailey et al. clearly illustrates that CD26^{high} T cells have a rich chemokine receptor profile, profound cytotoxicity, resistance to apoptosis and enhanced stemness (Bailey et al., 2017). These cells have a natural capacity to traffic to, survive in and regress solid tumors. Therefore, detection and quantification of intra-tumor CD26$^+$ T cells before and during immune therapy for cancer is highly needed to reveal its value as a predictive marker.

In the abovementioned studies, it is not always clear whether the immunohistochemistry staining of CD26 or mRNA expression data reflect tumor cell associated CD26 or CD26$^+$ infiltrating cells. Well validated multiplex assays are needed to explore this important issue.

5. Other family members of DPP4 in cancer

While DPP4 and FAP have been extensively investigated in multiple cancer types, the related family members, DPP8 and DPP9, have received far less attention. However, they also need to be carefully considered as more information on their role in cancer is being uncovered. Most articles on DPP8 and DPP9 focus mainly on their (altered) expression in several tumors, though in recent years, evidence pointing

towards a role in cell death is rapidly expanding. A remark needs to be made when interpreting data from expression and functional studies in the field of dipeptidyl peptidases. As the individual enzymes were discovered over multiple decades, it is likely that the antibodies, substrates or inhibitors used in the past might not have been selective. Even up to now, there is still a lack of selective substrates and inhibitors that can effectively distinguish between DPP8 and DPP9. These enzymes are reported as a joint DPP8/9-activity after the addition of a selective DPP8/9-inhibitor. Furthermore, a number of articles describe a DPP4-like activity, which can include DPP4-, 8-, 9- and FAP activity. DPP2 has similar preferences regarding synthetic substrates, yet it prefers a more acidic pH for its activity and hence its interference can be eliminated in biochemical assays using the appropriate buffer. DPP4-like enzymatic activity can be measured with colorimetric substrates, such as glycyl-prolyl-*para*-nitroanilide (Gly-Pro-*p*NA), or with fluorometric substrates. In blood, this assay selectively measures DPP4 activity, as demonstrated in (Matheeussen et al., 2012). However, it should be noted that it is possible that in disease states other enzymes could also play a role because of different mechanisms. In most cases, the specificity of activity assays was not confirmed with a selective DPP4 inhibitor. In this next section, we provide a comprehensive overview of all available human data on the expression and/or activity of DPP8 and DPP9 in cancer. For an overview of FAP in cancer, we refer to (Puré & Blomberg, 2018).

5.1. Expression and activity of DPP8 and DPP9 in cancer

DPP8 and DPP9 enzymatic activity, mRNA and/or protein expression have been reported in cell lines from various types of cancer, such as hepatocellular, breast, epithelial ovarian carcinoma and also in different leukemia cell lines (Ajami et al., 2004; Chowdhury et al., 2013; Maes et al., 2007; Matheeussen et al., 2013; Wilson & Abbott, 2012; Yu et al., 2009). In addition, a comprehensive overview can be found in the Human Protein Atlas. Based on RNA-seq data from The Cancer Genome Atlas project, DPP9 was categorized as an unfavorable prognostic marker in renal cancer, while it is considered to be a favorable prognostic marker in endometrial, stomach and breast cancer (The Human Protein Atlas, 2018d). DPP8, in contrast, is not labeled as a prognostic marker (The Human Protein Atlas, 2018c). In B-CLL, DPP8 mRNA expression was increased in B-CLL lymphocytes compared to normal tonsil B lymphocytes, while DPP9 mRNA tended to be decreased, although this was not significant (Sulda, Abbott, Macardle, Hall, & Kuss, 2010).

In different types of brain tumors, such as astrocytic tumors and meningiomas, DPP8 and DPP9 mRNA and protein could be detected (Busek et al., 2012; Šedo et al., 2004; Stremenová et al., 2007, 2010). Based on the use of discriminating inhibitors, it can be concluded that in astrocytic tumors, DPP4-like activity increased with tumor grade (Stremenová et al., 2007). The opposite is true for atypical meningiomas, where the DPP4-like activity most likely can be attributed to DPP8 and DPP9 (Stremenová et al., 2010).

DPP9 has also been shown to be involved in gene fusions in serous ovarian carcinoma (Smebye et al., 2017). RNA-sequencing identified two fusion transcripts (one of DPP9 with protein phosphatase 6 regulatory subunit 3, and one with perilipin 3). These rearrangements would lead to a decreased expression of the 3' end of DPP9, which could result in the loss of the active domain of DPP9. A third rearrangement of DPP9, in this case with paired box protein Pax-2, in high-grade serous ovarian carcinoma was reported by Hoogstraat et al., again resulting in the loss of the 3' end (Hoogstraat et al., 2014). In ovarian clear cell adenocarcinoma DPP9 was also identified as a gene with copy number aberrations and lowered expression (Sung et al., 2013). Additionally, DPP8 and DPP9 mRNA was shown to be higher in effusions compared to solid lesions in ovarian carcinoma of all histotypes and in high-grade serous ovarian carcinoma separately (Brunetti et al., 2019). DPP9 mRNA was also higher in high-grade serous ovarian carcinoma versus the other histotypes. Protein expression of DPP8 was higher in high-grade serous carcinoma effusions of patients with complete response to chemotherapy at the time of diagnosis. DPP8 and DPP9 mRNA and protein expression was not related to survival in the effusion cohort. In contrast, higher DPP9 mRNA levels in pre-chemotherapy effusions were related to longer overall survival (Brunetti et al., 2019). DPP8 was found to promote tumor growth in primary MMTV-ErbB2 mammary tissue (Huo, Su, Cai, & Macara, 2016). Recent work from Chen et al. studied the expression of DPP8 in cervical cancer (Y. Chen et al., 2018). First, a microarray dataset was extracted from the Oncomine database and the Human Protein Atlas was consulted. Based on these datasets, researchers reported a higher DPP8 expression in cervical cancer compared to normal cervical tissue. However, a statistical analysis and explanation of the chosen cut-off value is missing. In addition, the expression was also evaluated with real-time PCR, western blot and immunohistochemistry on cancer samples and a higher expression was found in the tumor samples compared to adjacent normal cervical tissue (Chen et al., 2018). In human prostate cancer lines, the aggressive cell lines PC3 and DU145 had higher DPP9-activity when compared to the less aggressive cell line LNCaP (Nomura et al., 2011). In contrast, only a small non-significant increase of DPP8-activity was seen in these aggressive cell lines. DPP8-activity was differentiated from DPP9-activity by the use of an activity-based protein profiling approach combined with LC-MS (Nomura et al., 2011). In testicular tumors ($n = 4$) DPP9 mRNA expression was increased compared to normal testes (pool from 23 individuals) (Yu et al., 2009).

It has also been suggested that DPP9 plays a role in NSCLC (Tang et al., 2017). Tang and colleagues showed that DPP9 mRNA expression was higher in NSCLC tissues ($n = 30$) compared to adjacent non-cancerous tissues. Immunohistochemistry ($n = 217$) showed staining for DPP9 localized to the cellular membrane and cytoplasm in tumor tissues, with lower a staining intensity in normal lung tissue. Furthermore, overexpression of DPP9 was associated with lymph node and tumor node metastasis (TNM) and was a negative prognostic factor for 5-year overall survival.

5.2. DPP8 and DPP9 in cell death and proliferation

Throughout the years, multiple studies have been published suggesting a role for DPP8 and DPP9 in cell death and proliferation. However, some findings are contradictory and these will be discussed in the following part.

Cell death has been observed in cells in which DPP8 or DPP9 was overexpressed. For example, DPP8-cyan fluorescent protein (CFP)- and DPP9-CFP-transfected HEK293T cells showed increased staurosporine streptomyces-induced apoptosis compared to cells transfected with CFP alone (Yu, Wang, McCaughan, & Gorrell, 2006). Furthermore, enzyme-negative mutants showed the same effect, indicating that the enzymatic activity is not necessary for the induction of cell death. For both the active and inactive DPP9 constructs, it could even be observed without staurosporine streptomyces treatment (Yu et al., 2006). In HepG2 cells, overexpression of DPP9 caused intrinsic apoptosis, showing higher levels of caspase-3 and -9 when compared to an enzyme negative mutant. Moreover, overexpression of DPP9 reduced Akt activation by epidermal growth factor, while the enzymatically inactive DPP9 mutant did not alter Akt phosphorylation in both HepG2 and Huh7 cell lines (Yao et al., 2011). Finally, DPP9 overexpression in Raji cells resulted in increased cell death, which was less pronounced when transfected with enzymatically inactive DPP9 (Chowdhury et al., 2013).

In contrast, multiple other studies describe cell death after the use of selective DPP8/9-inhibitors. For instance, in phorbol 12-myristate 13-acetate differentiated U937 cells and human monocyte-derived macrophages, the selective DPP8/9-inhibitor 1G244 induced spontaneous apoptosis (Matheeussen et al., 2013). Proliferation was inhibited in human peripheral blood mononuclear cells stimulated with phytohemagglutinin or superantigen (mixture of staphylococcal enterotoxins) when treated with the non-selective DPP inhibitor Val-boroPro or the DPP8/9-inhibitor *allo*-Ile-isoindoline (Lankas et al., 2005). In addition, in dermal fibroblasts and HaCat cells, survival and proliferative capacity was

reduced in the presence of 10 μM of 1G244 (Gabrilovac, Čupić, Zapletal, Kraus, & Jakić-Razumović, 2017). DPP9$^{ki/ki}$ mice are known to die within 8-24 hours after birth (Gall et al., 2013; Kim et al., 2017), and it has been stated that the cause of this neonatal lethality is due to a suckling defect, which in turn is the consequence of increased apoptosis of a certain type of progenitor cells, resulting in the abnormal formation of intrinsic muscles of the distal tongue (Kim et al., 2017). In the NSCLC study mentioned earlier, the researchers additionally reported that knockdown of DPP9 in the cell lines A549 and H1299 resulted in inhibited proliferation, cell motility and invasiveness in vitro. The decrease of DPP9 also resulted in altered epithelial-mesenchymal markers and increased apoptosis-related proteins in vitro. These results were repeated in vivo when the DPP9-knockdown cells were subcutaneously injected in BALB/c athymic nude mice, in addition to reduced tumor growth (Tang et al., 2017). Chen et al. additionally reported, that knockdown of DPP8 resulted in an increased number of early apoptotic cells, increased expression of BAX and reduced expression of cyclin D, Bcl-2, MMP2 and MMP9 in HeLa and SiHa cells. Furthermore, knockdown led to reduced proliferation, migration and invasion of these cancer cell lines (Y. Chen et al., 2018).

It has been shown that both the membrane-bound DPP4 and the cytosolic enzymes DPP8 and DPP9 are survival factors in the Ewing sarcoma family of tumors (ESFT) (Lu et al., 2011). Through cleavage of neuropeptide Y $(NPY)_{1\text{-}36}$ into $NPY_{3\text{-}36}$, which is inactive at the Y1 receptor, they protected ESFT cells from cell death. In this experimental set-up, the authors observed events consistent with apoptosis-inducing factor-mediated caspase-independent cell death.

The fact that DPP8 and DPP9 could be potential targets for the treatment of AML was initially suggested by Spagnuolo et al. (Spagnuolo et al., 2013). In the search for a compound that could synergistically enhance the cytotoxicity of parthenolide in the leukemia stem cell line TEX, they identified vildagliptin in a high-throughput screening assay. When evaluating the combined effect of the two compounds in primary AML patient samples (n=3) and the $CD34^+/CD38^-$ fraction of AML stem cells (n = 2), the combination enhanced cytotoxicity in all patient samples. In normal hematopoietic cells, the effect of vildagliptin/parthenolide on viability was less pronounced. Looking into the underlying mechanism, the primary target of vildagliptin, DPP4, was ruled out due to its absence on TEX cells. In addition to DPP4, vildagliptin also inhibits DPP8 and DPP9, albeit at higher concentrations (EMA, 2007). In the cell lines TEX and OCI-AML2, DPP8 and DPP9 mRNA could be detected and a double knockdown of these two enzymes resulted in a cytotoxicity, when treated with parthenolide that was comparable to the effect of vildagliptin addition. This was not the case with a single knockdown, suggesting that both enzymes play a role in the observed cell death. However, the exact mechanism behind these observations still needs to be elucidated and should be repeated on larger patient numbers. In this study, there wasn't a particular emphasis on the effect of vildagliptin alone on the AML cell lines or primary AML patient samples, because the authors specifically sought for a compound that could enhance the cytotoxicity of parthenolide. Nonetheless, controls with vildagliptin alone were included in these experiments and only a limited effect of the inhibitor could be seen on the viability in AML cell lines and primary samples. Likewise, the authors did not report a cytotoxic effect after knockdown of DPP8 and/or DPP9 in the absence of parthenolide (Spagnuolo et al., 2013).

More recently, the potential of DPP8/9-inhibitors in the treatment of AML was investigated by Johnson et al. (Johnson et al., 2018), after the observation that the non-selective DPP inhibitor Val-boroPro triggers a pro-inflammatory form of cell death called pyroptosis in murine and human monocytes and macrophages (Okondo et al., 2017; Taabazuing et al., 2017). In this case, the effect of the non-selective inhibitor is mediated through DPP8 and DPP9, as confirmed with knockouts and more selective inhibitors. Pyroptosis could be induced with DPP8/9-inhibitors in the majority of human AML cell lines and in primary AML cells. While Val-boroPro had no effect on a selection of non-AML cell lines, such as Jurkat and MCF-7. Both CARD8 and pro-caspase-1 are required for the induction of pyroptosis in human myeloid cells. In a patient-derived xenograft model of AML, Val-boroPro reduced the number of human AML cells in peripheral blood by approximately 75% compared to vehicle control (Johnson et al., 2018). The induction of this lytic form of cell death by DPP8/9-inhibitors, has also very recently been reported by another research group (F. L. Zhong et al., 2018).

The inhibitor Val-boroPro used in these pyroptosis experiments is not new and is also known as Talabostat, PT-100 or BXCL701. In animals, the inhibitor induced regression in different tumor models and its anti-tumor activity was reported to be immune mediated (Adams et al., 2004; Jesson et al., 2007; Walsh et al., 2013). More than a decade ago this pan-inhibitor of the DPPs already reached several phase 2 clinical trials, being studied in stage IV melanoma (Eager, Cunningham, Senzer, Stephenson, et al., 2009), advanced NSCLC (Eager, Cunningham, Senzer, Richards, et al., 2009) and metastatic colon cancer (Narra et al., 2007). However, these studies demonstrated no to minimal clinical effect of talabostat and phase 3 studies of talabostat in NSCLC were put on hold. Today, the compound has regained interest, especially in combination therapy in pancreatic and neuroendocrine prostate cancer (Rastelli et al., 2017; Rastelli, Gupta, Jagga, Charych, & Zalevsky, 2018) and in AML as stated above. Also other pan-inhibitors of the DPPs have been studied in cancer (Duncan et al., 2013).

Since their discovery almost two decades ago now, DPP8 and DPP9 have been studied in various cell types and cancers from different origins and although the current literature is not as large as it is for DPP4 or FAP, present data point towards a role for these enzymes in cancer. This can be as a biomarker, if their expression or activity is changed in cancerous tissue compared to normal tissue, or as a therapeutic target. However, presently, there is conflicting data and this is most likely due to the different cell or cancer types, experimental set-ups and reagents used. It might indicate different roles for these enzymes in different cell types or disease settings, or it could be an experimental artifact. In any case, more research needs to be done to validate the role of these enzymes in cancer. For now, their role in inducing pyroptosis in macrophages looks very promising and their potential as a therapeutic strategy in the treatment of AML should be further explored. Furthermore, it is possible that the role that each enzyme plays in cancer is not large enough for specific inhibitors to be used as a monotherapy. In this case, it could potentially be more effective to inhibit the entire DPP family to exploit their different roles in cancer, as has been done with talabostat, or to combine specific inhibitors with other types of cancer treatment.

6. Membrane-bound CD26/DPP4 as a biomarker in cancer

Considering the body of research to date on the role of CD26/DPP4 in malignancies, its value as a biomarker might best be categorized as a diagnostic as well as a prognostic marker in some cancers with one remarkable 'sub'category as a CSC marker, which recently has become a focus of interest. The function of CD26 as a CSC marker can be relevant in both biomarker categories. Firstly, CD26 executes a pro-oncogenic function in various cancers, thus exhibiting a potential negative prognostic value. Among hematological malignancies, CD26 negatively predicts outcome in B-CLL and possibly in T-anaplastic large cell cancer. However, in transformed mycosis fungoides, loss of CD26 expression on T helper cells was a negative prognostic factor (Vural et al., 2017) and might be of use for staging (Vonderheid & Hou, 2018). Moreover, $CD26^+$ CSCs in CLL are an independent prognostic factor for disease progression (Ibrahem, Elderiny, Elhelw, & Ismail, 2015) and in CML, presence of $CD26^+$ CSCs correlated with white blood counts at diagnosis (Culen et al., 2016), however, the relevance for survival still remains to be determined. Furthermore, the Human Protein Atlas reported a high DPP4 expression as a favorable prognostic marker in thyroid cancer (The Human Protein Atlas, 2018a; Uhlen et al., 2017). However, in contrast, high CD26/DPP4 expression was associated with the negative prognostic factors extrathyroideal extension, BRAF mutation and advanced tumor stage in papillary thyroid carcinoma (Lee et al., 2017).

CD26 expression is a potential positive prognostic factor as it is linked to increased chemotherapy sensitivity in malignant pleural mesothelioma (Aoe et al., 2012). In lung cancer and gynecological tumors, analysis for a possible correlation of CD26 expression with prognostic factors such as disease-free and overall survival still needs to be implemented. CD26 expression in ovarian cancer increased sensitivity for some chemotherapy agents (Kajiyama et al., 2010), however, it correlated with shorter overall survival in one study (Zhang et al., 2008). When evaluating CD26 as a biomarker in gastrointestinal malignancies, its most prominent role was found in CRC so far. $CD26^+$ CSCs showed a metastatic capacity, thus being a potential prognostic factor for histopathological risk assessment (Pang et al., 2010). Additionally, CD26 expression in CRC tissue correlated with tumor stage, grade and metastasis, predicting poor prognosis (Lam et al., 2014). Interestingly, a study performed on cancer tissue of rectal cancer patients after neoadjuvant chemoradiotherapy revealed that while CD26 expression in tumor tissue was associated with a poor pathological diagnosis, such as serosal or vascular invasion, CD26 expression in tumor stroma was significantly linked to relapse and prognosis in rectal cancer after neoadjuvant chemoradiotherapy (Saigusa et al., 2016). In gastric cancer stem cells, CD26 is a marker for their more invasive phenotype as a potential negative prognostic factor (Nishikawa et al., 2015), although further evidence is needed considering the limited data available. In esophageal cancer, similar to findings in lung cancer, CD26 expression might imply different prognostic consequences depending on the respective histological subtype. In adenocarcinoma of the esophagus, CD26 is overexpressed and linked to distant metastasis, a correlation with survival, however, still needs to be established. In contrast, an overexpression in esophageal SCC correlated positively with patient survival (Goscinski, Suo, Nesland, Florenes, et al., 2008). However, due to contradicting findings within the same research group varying with cohort size, these results need to be further verified. In HCC, the prognostic impact of CD26 expression remains to be clarified. Moreover, CD26 expression was reported as a negative prognostic factor in osteosarcoma (Zhang et al., 2013). The first study to establish a prognostic value of CD26 expression in urothelial cell cancer (Liang et al., 2016) showed that CD26/DPP4 overexpression is an independent prognostic biomarker for shorter disease-specific and metastasis-free survival among other factors, such as tumor stage, nodal metastasis and histological grade.

Secondly, CD26 seems to be linked to anti-oncogenic properties as a potentially positive prognostic factor in a smaller number of tumor entities. CD26 expression is known to be downregulated during malignant transformation in melanoma, however, further investigation is needed to evaluate the prognostic value. In human glioma, CD26 is overexpressed and seems to play a relevant anti-oncogenic role degrading CXCL12, a factor stimulating tumor growth. Interestingly, this same effect has been held accountable for its anti-oncogenic role in prostate cancer. Thus, in these cases, the downregulation of CD26 expression should be investigated as a negative prognostic predictor.

7. CD26/DPP4 in circulation

In addition to the cell-bound CD26/DPP4, a soluble form of CD26/DPP4 (sCD26/DPP4) can be found in body fluids. Next, we will therefore focus on work of the last decade which studied sCD26/DPP4 in serum or plasma or membrane-bound CD26/DPP4 on cells in the circulation, from patients with different cancer types. The expression of CD26/DPP4 on tumor cells is discussed earlier in this review. Protein levels or enzymatic activity of sCD26/DPP4 have been determined in serum or plasma using different techniques, such as ELISA and enzymatic activity measurements. Cell-bound CD26/DPP4 is typically measured by flow cytometry. Research preceding this time period is discussed in (Cordero et al., 2009; Šedo et al., 2008). An overview of the different studies that are discussed, can be found in Table 1.

7.1. Skin and eye cancer

Serum activity of DPP4 is decreased in patients with melanoma, compared to healthy controls and patients with vitiligo (Matić et al., 2012). Patients with other malignant skin tumors and benign skin changes were investigated, but due to limited sample size, it is difficult to draw solid conclusions from these data. Moreover, there was a significant decrease in the percentage of $CD26^+$ total white peripheral blood cells in patients with melanoma compared to controls. In addition, there was a significant decrease in the percentage of lymphocytes in melanoma patients. The observed differences were not dependent on the presence of metastatic disease. No differences were seen in the percentage of $CD26^+$ lymphocytes or in the mean fluorescence intensity of CD26/DPP4 expression on lymphocytes between the different groups. No conclusions were drawn about the possible use of the observed differences in the diagnosis or follow-up of melanoma (Matić et al., 2012). In uveal malignant melanoma an increase in DPP4 activity has been reported, however this was a pilot study with a limited sample size and follow-up studies are needed to fully determine CD26/DPP4's potential as a marker for diagnosis or prognosis (Varela-Calviño et al., 2015).

7.2. Lung cancer

In the search for a marker panel that could identify patients with a high-risk for lung cancer, sCD26/DPP4 was evaluated, together with the soluble form of epidermal growth factor receptor, epidermal growth factor, heparin-binding epidermal growth factor, vascular endothelial growth factor and calprotectin (Blanco-Prieto et al., 2015). Serum sCD26/DPP4 was reduced in these lung cancer patients compared to healthy controls and patients with benign pulmonary pathologies. In addition, levels were lower in advanced NSCLC stages compared to control, but not in early stages. Based on the performance of all six markers, sCD26/DPP4, epidermal growth factor and calprotectin were selected for further evaluation. This marker panel reached a sensitivity of 83% and a specificity of 87% with an associated misclassification rate of 15% for the detection of lung cancer (Blanco-Prieto et al., 2015) thus illustrating the potential of adding CD26/DPP4 to a multiplex panel.

7.3. Malignant pleural mesothelioma

MPM is an aggressive malignancy with a poor prognosis, and it has been shown that both serum sCD26/DPP4 levels and enzymatic activity were decreased in these patients as compared to patients with past asbestos exposure (Fujimoto et al., 2014). Again, serum protein levels were decreased in patients with advanced stages of MPM compared to earlier stages, but there was no difference in enzymatic activity. Patients with a higher DPP4 enzymatic activity had a longer median overall survival than those with lower enzymatic activities, whereas no difference in overall survival was seen when protein levels were compared. In pleural fluid, higher protein levels and enzymatic activity was detected in MPM patients with an epithelioid subtype, in comparison to patients with benign pleural diseases. Protein levels of sCD26/DPP4 were also higher in the epithelioid subtype compared to the sarcomatous subtype, a non-significant increase was seen for the enzymatic activity. Overall survival did not differ according to the protein levels or the enzymatic activity, however, survival was significantly prolonged in patients with a lower specific enzymatic activity, defined as the DPP4 enzymatic activity over the protein level in pleural fluid. Based on these results, it can be concluded that sCD26 levels or DPP4 activity in pleural fluid could be used as a diagnostic marker for the epithelial subtype of MPM and that the serum DPP4 activity and the specific DPP4 activity in pleural fluid could be a prognostic factor in patients with MPM (Fujimoto et al., 2014).

Table 1
Overview of the different studies performed on (soluble) CD26/DPP4 in the circulation in cancer. Samples were serum or plasma for sCD26/DPP4 or whole blood for cell surface expression of CD26/DPP4. For a comprehensive discussion, refer to the text.

Cancer type	Control groups	Methodology	Main findings	Ref.
Melanoma	- Melanoma (n = 64) - Vitiligo (n = 16) - Other malignant skin tumors (n = 6) - Benign skin changes (n = 6) - Healthy controls (n = 40)	- Enzymatic activity with Gly-Pro-*p*NA - Flow cytometry (BD, № 340423, clone L272)	- ↓ in serum activity in melanoma patients compared to controls and vitiligo patients - ↓ % of $CD26^+$ total white blood cells in melanoma patients - ↓ % lymphocytes in melanoma patients	(Matić et al., 2012)
Lung cancer	- Lung cancer patients (Total: n = 72; NSCLC: n = 64; SCLC: n = 8) - Benign pulmonary pathologies (n = 31) - Healthy controls (n = 24)	sCD26 ELISA (eBioscience)	- ↓ sCD26 in lung cancer patients compared to healthy controls and patients with benign lung pathologies - ↓ levels in NSCLC patients with disseminated stages versus controls, but not early stages	(Blanco-Prieto et al., 2015)
Malignant pleural mesothelioma (MPM)	- MPM patients (n = 80) - Patients with past asbestos exposure and pleural plaques (SPE; n = 79) - Other benign pleural diseases (OPD; n = 134)	- In-house developed and validated ELISA (clones 5F8/9C11) - Enzymatic activity with Gly-Pro-*p*NA	- ↓ CD26 serum levels in patients with MPM compared to SPE - ↓ DPP4 activity in patients with MPM compared to SPE - ↓ CD26 serum levels in stages III and IV compared to stages I and II - Median overall survival ↑ in MPM patients with higher DPP4 activity, but no difference in overall survival based on serum levels	(Fujimoto et al., 2014)
Breast tumors	- Malignant breast tumors (n = 69) - Benign breast tumors (n = 34) - Healthy controls (n = 24)	- Enzymatic activity with Gly-Pro-*p*NA - Flow cytometry (BD, № 340423, clone L272)	- Serum DPP4 activity = - ↓ % $CD26^+$ total white peripheral blood cells in both benign and malignant tumors versus control - % $CD26^+$ lymphocytes = - ↓ in mean fluorescence intensity of CD26 on lymphocytes in patients with malignant breast tumors versus control	(Erić-Nikolić et al., 2011)
Colorectal cancer (CRC)	- CRC (n = 33) - Polyps (n = 108) - Inflammatory bowel disease (IBD; n = 26) - Non-IBD (n = 64) - No colorectal pathology (n = 68)	sCD26 ELISA kit (Bender Medsystems)	- ↓ in serum sCD26/DPP4 levels in patients with IBD, CRC and anemia - Relationship between sCD26/DPP4 and presence of advanced adenomas (and grade of dysplasia, but non-significant) - Interesting for early diagnosis and screening of CRC and advanced adenomas	(De Chiara et al., 2010)
Colorectal cancer	Training set: - CRC (n = 68) - Non-cancer controls (n = 92) Testing set: - CRC (n = 38) - Non-cancer controls (n = 41)	sCD26 ELISA (Bender Medsystems)	- Training set: ↓ in sCD26/DPP4 in patients compared to controls (also when combined with testing set) - In combination with other markers, only modestly better than carcinoembryonic antigen alone, particularly in early stage cancers	(Shimwell et al., 2010)
Colorectal cancer	- CRC (n = 179) - Advanced adenoma (n = 193) - Participants free of colorectal neoplasm (n = 225)	sCD26 ELISA (Bender Medsystems)	- ↓ in sCD26/DPP4 in CRC patients compared to controls, but restricted to stage II, III and IV CRC - No statistically significant difference between advanced adenomas and controls - Not an alternative to FOBT-based CRC screening, but potentially as a combination	(Tao et al., 2012)
Colorectal cancer	- Asymptomatic individuals with at least one first-degree relative with CRC (n = 516)	Human sCD26 platinum ELISA kit (eBioscience)	- ↓ in serum CD26/DPP4 concentration in advanced adenoma and CRC (however, the latter non-significantly since n = 4) - Combination of serum sCD26/DPP4 could be interesting for the detection of advanced adenomas or CRC in familial-risk CRC screening	(Otero-Estévez et al., 2015)
Colorectal cancer	- CRC (n = 43)	Human sCD26 ELISA kit (eBioscience)	- sCD26/DPP4 levels during follow-up showed well-defined patterns in patients without disease, patients with tumor persistence, local recurrence or distant metastasis	(De Chiara et al., 2014)
Gastric cancer	- Gastric adenocarcinoma (n = 30) - Healthy controls (n = 24)	Human CD26/DPP4 ELISA kit (Boster Biological Technology)	- ↓ serum sCD26 levels in patients - Serum levels in HER2 positive tumors < HER2 negative tumors - Levels were independently associated with gastric cancer presence - Increase of serum levels 3 months after surgery	(Boccardi et al., 2015)

(continued on next page)

Table 1 (*continued*)

Cancer type	Control groups	Methodology	Main findings	Ref.
Esophageal squamous cell carcinoma (ESCC)	- Patients with ESCC (n = 254) - Healthy controls (age- and gender--matched; n = 254)	CD26 ELISA (Boster Biological Technology)	- sCD26 serum levels compared to controls: - ↓ at admission - = one month after surgery - ↓ at time of tumor relapse - Serum level < 530 pg/mL associated with poor prognosis Survival advantage with levels ≥ 530 pg/mL	(Xinhua et al., 2016)
Hepatocellular carcinoma (HCC)	- Patients with hepatitis B virus--related HCC (n = 210)	- DPP4-Glo Protease Assay (Promega)	- High serum CD26/DPP4 activity associated with poor clinical prognosis	(Qin et al., 2018)
Hepatocellular carcinoma	- Cause of hepatocellular carcinoma: o Hepatitis C infection (n = 21) o Hepatitis B infection (n = 11) o Alcoholic (n = 6) o Unknown (n = 3)	- DPP4 activity assay kit (BioVision)	- CD26 expression was associated with increased serum DPP4 activity - Significant decrease in serum DPP4 activity after surgical resection	(Nishina et al., 2019)
Pancreatic cancer	- Pancreatic ductal adenocarcinoma (PDAC, n = 92) - Healthy controls (n = 86)	- Human sCD26 Platinum ELISA kit (eBioscience)	- Higher preoperative sCD26/DPP4 levels compared to controls, but lower postoperative levels - Higher levels in patients with tumors located at the head of the tumor, with smaller tumor size, without metastasis and earlier TNM stages - Lower levels are associated with poorer postoperative survival	(Ye, Tian, Yan, et al., 2016)
Pancreatic cancer	- PDAC (n = 93) - Type 2 diabetes mellitus (T2DM, n = 39) - Healthy controls (n = 29)	- Enzymatic activity with Gly-Pro-7-amido-4--methylcoumarin - CD26 DuoSet ELISA (R&D)	- Non-significant higher activity in PDAC patients compared to T2DM patients and healthy controls - Significant lower protein levels in PDAC patients compared to T2DM patients, which are non-significantly higher in comparison to controls - Specific sCD26/DPP4 activity significantly higher in PDAC patients compared to T2DM patients, but similar to controls	(Busek et al., 2016)
Prostate cancer	- Localized prostate carcinoma (n = 48) - Metastatic prostate carcinoma (n = 48) - Men with no known malignancies (age-matched; n = 48)	- Activity assay with Arg-Pro-peptide and a MALDI-TOF MS read-out - Human CD26/DPP4 Quantikine ELISA kit (R&D, DC260)	- Serum DPP4 activity ↓ in metastatic disease patients compared to patients with localized disease and healthy controls - Protein levels = in all three groups - Presence of a blood-based inhibitor of sCD26/DPP4 in patients with metastatic disease - Predictor of cancer status and metastatic disease	(Nazarian et al., 2014)
Ewing sarcoma (ES)	- ES (n = 232) - Osteosarcoma (n = 21) - Healthy controls (n = 31)	- Enzymatic activity with Gly-Pro-*p*NA	- No differences in DPP4 activity in ES patients compared to the other groups - Higher levels of sCD26/DPP4 were associated with longer event-free survival in ES patients with localized disease	(Tilan et al., 2015)
Cancer	- Breast cancer (n = 56) - Hematological cancer (n = 28) - Head and neck cancer (n = 55) - Colorectal cancer (n = 88) - Lung cancer (n = 100) - Prostate cancer (n = 45) - Gynecological cancer (n = 100) - Upper gastrointestinal, liver and pancreas cancer (n = 27) - Other/unknown cancer (n = 62) - Healthy controls (n = 139)	In-house made ELISA with monoclonal antibody pair of E26 and E3	- ↓ in plasma sCD26/DPP4 levels in all cancer patients combined compared to control - Significantly lower levels in gynecological, hematological, head and neck, lung, colorectal and upper gastrointestinal cancers compared to control - ↓ in sCD26/DPP4 in TNM stage III compared to I, II and IV - Lower sCD26/DPP4 is all cancers combined associated with significantly shorter survival (and in head and neck cancer)	(Javidroozi et al., 2012)

7.4. Breast cancer

Serum activity and CD26/DPP4 expression on lymphocytes was determined in patients with benign and malignant breast tumors and in healthy controls (Erić-Nikolić et al., 2011). The heterogeneous CD26 expression in breast cancer might explain why the DPP4 activity in serum of patients revealed no statistical difference with healthy controls. There was a significant decrease in the percentage of CD26/DPP4 positive cells in total white peripheral blood cells from patients with benign or malignant tumors compared to controls. However, there was no significant difference in the percentage of CD26/DPP4 positive lymphocytes. A significant decrease in mean fluorescence intensity of CD26 expression on lymphocytes was found in the group with malignant breast tumors in comparison to controls. No further research was done on the possible benefit of measuring these parameters in breast tumors (Erić-Nikolić et al., 2011).

7.5. Gastro-intestinal cancers

7.5.1. Colorectal cancer

Quite some work has been done on sCD26/DPP4 in CRC. Multiple studies show a decrease in serum sCD26/DPP4 protein levels in CRC patients compared to controls and certain studies also report a decrease in advanced adenomas (Ayude et al., 2004; Cordero, Ayude, Nogueira, Rodriguez-Berrocal, & de la Cadena, 2000; De Chiara et al., 2010; Otero-Estévez et al., 2015; Shimwell et al., 2010; Tao, Haug, Kuhn, & Brenner, 2012). It should, however, be noted that the exact composition of the control group is very diverse between the different studies. In addition, these studies often do not offer a direct comparison with patients with other colorectal pathologies, such as for example inflammatory bowel disease (IBD). De Chiara et al. did include IBD-patients in their study and also measured a lower sCD26/DPP4 level in these patients compared to controls (De Chiara et al., 2010). This observation has also been reported in independent studies (Hildebrandt et al., 2001; Magro et al., 2017). Another interesting finding from this study was that patients with anemia had lower sCD26/DPP4 compared to the other non-colorectal pathology patients. The differential expression of sCD26/DPP4 in CRC and advanced adenomas, of course, triggers an interest for sCD26/DPP4 as a biomarker, which has consequently also been studied, either alone or in combination with other screening tests. As a decrease in serum sCD26/DPP4 is not specific for CRC, it will rather be of additional value when used in combination with other tests (Cordero et al., 2011). sCD26/DPP4 has also been studied as a marker of recurrence of CRC, stating that the levels of serum sCD26/DPP4 followed well-defined patterns in patients without disease, patients with tumor persistence, local recurrence or distant metastasis. For example, disease-free patients would increase to normal and stable levels, while patients with recurrent tumors showed unstable levels with large increases and decreases. The authors therefore suggest that it could be used for the early detection of local and distant recurrence. However, the sample size was small and a larger study should be done to confirm these findings (De Chiara et al., 2014).

7.5.2. Gastric cancer

In gastric cancer, serum sCD26/DPP4 protein levels were decreased compared to healthy controls (Boccardi et al., 2015). Moreover, patients with HER2 positive tumors had lower sCD26/DPP4 levels compared to patients with HER2 negative tumors. Serum levels rose again three months after surgery and reached levels similar to the control group. The authors suggest that serum sCD26/DPP4 could be an early detection marker for gastric cancer and possibly serve as a prognostic marker (Boccardi et al., 2015).

7.6. Esophageal cancer

Serum levels of sCD26/DPP4 have been determined in esophageal SCC as well (Xinhua et al., 2016). Once again, protein levels were decreased in patients compared to healthy controls and recovered to normal values one month after tumor resection. In case of tumor relapse serum sCD26/DPP4 decreased again. Lower levels were associated with poor prognosis in esophageal SCC patients and a survival analysis also demonstrated a significant survival advantage for patients in the high sCD26/DPP4 level group (≥ 530 pg/mL as measured by ELISA). The authors conclude that sCD26/DPP4 might not be a diagnostic indicator, but that it could serve as an independent prognostic indicator in esophageal SCC patients and that it might be useful in detecting recurrent ECSS (Xinhua et al., 2016).

7.7. Hepatocellular carcinoma

Next to the experimental work done by Qin and colleagues, this group also measured serum CD26/DPP4 in patients with HCC and found that high CD26/DPP4 activity was associated with poor clinical prognosis (Qin et al., 2018). Nishina et al. showed that CD26/DPP4 expression in HCC specimens was associated with increased serum CD26/DPP4 activity and the activity decreased significantly after HCC resection (Nishina et al., 2019).

7.8. Pancreatic cancer

Pre- and postoperative levels of sCD26/DPP4 have been measured in the serum of pancreatic ductal adenocarcinoma patients (PDAC) (Ye, Tian, Yan, et al., 2016). The preoperative levels were higher compared to healthy controls. Higher sCD26/DPP4 levels were seen in patients with tumors located at the head of the pancreas, with smaller sized tumors, without metastasis and in earlier TNM stages. Patients with a lower sCD26/DPP4 level had a poorer postoperative survival. Serum sCD26/DPP4 did not appear to be usable for the diagnosis of PDAC patients. In contrast, postoperative levels were significantly decreased compared to healthy controls (Ye, Tian, Yan, et al., 2016). Busek et al. also measured the activity and concentration of sCD26/DPP4 in the plasma of PDAC patients (Busek et al., 2016). The authors found a non-significant increase in the activity in PDAC patients compared to T2DM patients and healthy controls. Conversely, the protein levels of sCD26/DPP4 were significantly lower compared to T2DM patients but were non-significantly higher in comparison to healthy controls. The 'specific sCD26/DPP4 activity', which is the ratio of the enzyme activity over the protein level, was significantly higher in PDAC patients than in T2DM patients, but was similar to the value of the control group (Busek et al., 2016). In the past, clinically used DPP4 inhibitors have been linked with pancreatic cancer. However, recent meta-analyses did not find an association between DPP4 inhibitors and pancreatic cancer (Chen et al., 2016; Pinto, Barkan, Leitão, & Gross, 2018).

7.9. Prostate cancer

Starting from a broader approach in mouse models of prostate cancer, DPP4 was reduced in mice with progressive invasive prostate cancer (Nazarian et al., 2014). With a MALDI-TOF MS method for measuring DPP4 enzymatic activity in serum samples of prostate cancer patients and a healthy control group, it was seen that patients with metastatic disease had decreased activity when compared to patients with localized disease and the control group. However, protein levels, measured with ELISA, were not different between the three groups, which suggests differences in post-translational modifications, allosteric changes or an endogenous DPP4 inhibitor. Further experiments performed by the authors point towards the presence of a low-molecular-weight endogenous inhibitor of DPP4, which has not been specified any further. After adjusting for total prostate-specific antigen, DPP4 activity was a significant predictor of cancer status (healthy versus cancer patient) and of patients with localized versus metastatic disease. Therefore, DPP4 activity could be used alone or in combination, the latter being more likely, with other markers of prostate cancer as an indicator of metastatic disease (Nazarian et al., 2014).

7.10. Other tumor entities

In Ewing sarcoma, an aggressive malignancy in children and adolescents, no significant differences were found in the DPP4 enzymatic activity compared to patients with osteosarcoma or healthy controls (Tilan et al., 2015). Nevertheless, there was a significant effect on event-free survival in Ewing sarcoma patients with localized disease, meaning that higher sCD26/DPP4 activity is associated with a better event-free survival. A non-significant trend was seen with overall survival. The authors suggest that high sCD26/DPP4 activity might reflect a more efficient immune response that inhibits disease progression (Tilan et al., 2015).

A study in which plasma sCD26/DPP4 levels were determined in various types of cancer, including breast, hematological, head and neck, colorectal, lung, prostate, gynecological, upper intestinal, liver and pancreas and other/unknown cancers, reported lower levels in cancer patients as compared to healthy controls (Javidroozi, Zucker, & Chen, 2012), which could also be found when the analysis was repeated with age-matched subjects. However, no significant differences in sCD26/DPP4 protein levels were found in the prostate and breast cancer subgroups. sCD26/DPP4 levels were significantly lower in patients with TNM stage III compared to stages I, II and IV. In patients from whom a second sample was taken after surgery (median time elapsed was 7 days), no difference was seen between the first and second measurement, which indicates that the contribution of the tumor the circulating DPP4/CD26 is small or that the enzymes have long half-lives. Survival was shorter in patients with a lower sCD26/DPP4 level, in the subgroups analysis, this was also found for head and neck cancer (Javidroozi et al., 2012).

For the evaluation of CD26/DPP4 as a biomarker in the circulation, there are multiple approaches to measure CD26/DPP4: one can measure the enzymatic activity or the protein level of the soluble form by individual ELISAs or as a part of a multiplex immunoassay. Blood-cell membrane-bound CD26 is evaluated by flow cytometry. The different measurements are not necessarily correlated to each other and it is important to keep this in mind when comparing data from different experiments (Cordero et al., 2009). Most articles indeed only focus on enzymatic activity and/or protein level of sCD26/DPP4 and/or on the CD26/DPP4 expression on the cell surface.

At the moment, it is impossible to come to one all-encompassing conclusion on the usefulness of CD26/DPP4 as a blood-based biomarker in cancer, as varying types of cancers have been assessed in different settings and with different goals. This illustrates the need for future well-designed studies. Multiple studies only include a control group consisting of healthy persons, not taking into account other non-malignant diseases that might present themselves with similar symptoms. In addition, patient groups often comprise a variety of subgroups of a certain cancer type, for example leukemia. This further complicates the comparison between different studies. Another frequently observed drawback of these studies is the limited size of several patient groups. Moreover, in multiple cancers a decrease in serum levels or enzymatic activity of sCD26/DPP4 could be seen. Furthermore, a decrease is not only limited to cancer, but it has also been reported in other conditions (Cordero et al., 2009). Additionally, the decrease in sCD26 is not as pronounced and there is mostly still some considerable overlap between patients and controls. All of these factors limit its use as a diagnostic biomarker on its own for a specific type of cancer. As a prognostic marker, an increased activity or expression of CD26/DPP4 is in most cases associated with an improved prognosis, with hepatocellular cancer seemingly as an exception. It could also be useful to measure (soluble) CD26/DPP4 longitudinally as it might indicate whether a patient responds to a specific therapy or when the disease returns, but data on is this subject is scarce. To conclude, a lot of research has been done in the last decade on (soluble) CD26/DPP4 in circulation as a cancer marker, but there is still a need for high quality studies. Therefore, future research on the usefulness of CD26/DPP4 as a blood-based biomarker should include large patient groups, relevant controls and measurements of both the protein levels and activity of the soluble form as well as the expression of the membrane-bound form on cells in the circulation. Also, follow-up studies should be initiated. When assessing CD26/DPP4 expression on leukocytes, it is important to analyze flow cytometric data properly and to distinguish between cells with low, intermediate and high CD26/DPP4 expression as they reflect functionally distinct cells (Bailey et al., 2017; Vliegen & De Meester, 2018; Waumans et al., 2015). Combining CD26/DPP4 with other markers will probably have the greatest chance of success in identifying CD26/DPP4 as an effective biomarker in the diagnosis, prognosis or follow-up of a patient, and the exact combination will be dependent on the suspected disease. It can also have its use as a first less invasive test, being indicative for the need of more invasive testing. Moreover, during the last decade a lot of technical progress has been made with multiplex assays, facilitating the use of multimarker panels in the diagnosis, prognosis or follow-up of cancer patients.

8. Targeting CD26/DPP4 in cancer treatment

When considering a possible impact of CD26/DPP4 inhibitors on the presence or the development of cancer in diabetic patients, it seems obvious to take a closer look at patients with a long-standing history of inhibitor intake and cancer prevalence and incidence. In 2018, Overbeek and colleagues presented a meta-analysis investigating the correlation between site-specific cancer and the intake of DPP4 inhibitors (Overbeek et al., 2018). Although the follow-up time of 1.5 years was rather short, the authors could not conclude whether DPP4 inhibitors had any effect on site-specific cancer. Several research groups investigated potential mechanistic pathways for how cancer could be treated by a DPP4 inhibitor. MPM is known to express relatively high amounts of DPP4 (Aoe et al., 2012) . The well experienced research group around Morimoto analyzed the effect of targeting the CD26 molecule with a humanized anti-CD26 mAb, focusing particularly on ubiquitin-specific protease 22 (USP22) in human specimens. This antibody treatment induced a decrease in USP22 level, leading to increased levels of ubiquitinated histone H2A and p21 and suppression of MPM cell proliferation. (Okamoto et al., 2018). An increased expression of DPP4 was also observed in other malignancies as discussed above. In both rat and mice preclinical models, the inhibition of DPP4 activity by vildagliptin resulted in the prevention of HFD-induced liver cancer angiogenesis by interfering with HFD-induced C-C motif ligand (CCL)2 upregulation (Qin et al., 2018). This finding corroborates with earlier reports that CCL2 promotes tumor angiogenesis via a crosstalk between CCL2 and macrophages (Arendt et al., 2013) and that CCL2 directly recruits macrophages to facilitate tumor metastasis (Qian et al., 2011). CCL2 is a natural substrate of DPP4 and it is currently not clear how exactly DPP4 inhibition is linked to a decrease in CCL2 level. More complex mechanisms may underlie the observed in vivo protective effects of vildagliptin. A clinical study applying vildagliptin in HCC is planned (Qin et al., 2018).

Apart from CCL2, also other peptide substrates of DPP4 such as glucagon-like peptide-2, CXCL5 and CXCL12, can be associated with tumor development and progression. Sitagliptin significantly suppressed the levels of plasma CXCL5 and CXCL12 in mice fed a HFD which could suggest a reduction in cancer risk in obese or diabetic patients (Fujiwara et al., 2017).

In light of the increased risk of colon cancer in T2DM patients compared to those without diabetes, it is of interest to test the effect of DPP4 inhibitors on the development of colon cancer. Yorifujy and coworkers evaluated the effect of the DPP4 inhibitor sitagliptin, on diabetes-related mouse colon carcinogenesis and proteomic changes (Yorifuji et al., 2016). The authors demonstrated that long-term administration of sitagliptin had protective effects against colorectal neoplasia in T2DM mice, mainly via suppression of tumor-promoting IL-6. Without particularly providing mechanistic details, others confirmed the tumor-suppressing effect of sitagliptin in a rat colon cancer model (Femia et al., 2013). Our own group showed that the growth of pulmonary metastases from intravenously induced colon cancer cells could be

suppressed by the DPP4 inhibitor vildagliptin via a downregulation of autophagy which resulted in an increased apoptosis and a regression of the cell cycle (Jang et al., 2015). In an intriguing study, Barreira da Silva and colleagues used a tumor-transplant model of mouse melanoma to demonstrate that DPP4 mediated processing of CXCL10 diminished lymphocyte migration (Barreira da Silva et al., 2015). The biological activity of CXCL10 was preserved by sitagliptin which in turn resulted in a CXCL10–mediated infiltration of lymphocytes, mainly by T cells, into the tumor parenchyma resulting in diminished tumor growth. Moreover, by employing a triple therapy involving sitagliptin and the checkpoint-inhibitors anti-CTLA-4 and anti-PD-1, these authors convincingly showed a 100% rejection of murine colon cancer (CT26) tumors (Barreira da Silva et al., 2015). In line with this study, Nishina and colleagues showed that DPP4 inhibition of the $CD26^+$ HCC cell lines Huh-7 and Li-7, as well as on xenografted tumors, prevented truncation of the biologically active form of CXCL10 that binds to CXC3 on NK cells thereby enhancing NK- and T cell chemotaxis and suppressing tumor growth (Nishina et al., 2019).

The concept of preserving CXCL10 levels by DPP4 inhibition has also been readily achievable in humans (Decalf et al., 2016). These findings open opportunities for the use of DPP4 inhibitors in combination with checkpoint inhibitors. The anti-tumorigenic effect of sitagliptin was also tested in breast cancer. Choi and colleagues showed that the expression of DPP4 is positively correlated with the expression of PIN1, a phosphorylation signaling regulator that controls cell proliferation and transformation in human breast cancer tissues and promotes epithelial cell transformation (Choi et al., 2015). Sitagliptin suppressed epithelial cell transformation and mammary epithelial tumorigenesis via the inhibition of PIN1 expression, indicating that DPP4 might act upstream of PIN1 signaling. In contrast, no effect on in vitro breast cancer cell proliferation could be observed when using the DPP4 inhibitor linagliptin (Iwaya et al., 2017).

Experimental work on cell lines and also on human thyroid carcinoma samples using a DPP4 inhibitor or DPP4 silencing revealed that by DPP4 silencing, colony foci, cellular migration, and invasion were decreased via the TGF-β signaling pathway (Lee et al., 2017). Yang and colleagues demonstrated that DPP4 overexpression in endometrial carcinoma resulted in an altered cell morphology and cell proliferation, invasion and tumorigenesis both in vitro and in vivo. These effects were abrogated by DPP4 knockdown or pharmacological inhibition by sitagliptin via increased hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factor A (VEGFA) expression thereby promoting HIF-1α-VEGFA signaling (Yang et al., 2017). Apart from solid organ tumors, the effect of inhibiting DPP4 in chronic myeloid leukemia was studied and it was found that DPP4 inhibition suppressed the function of the oncogenic BCR/ABL1 positive cells (Herrmann et al., 2014).

Overall, mechanistic data on patients undergoing treatment with a DPP4 inhibitor for diabetes, and who also have a tumor, are scarce. A case report mentions signs of progression of a carcinoid tumor after initiation of DPP4 inhibitor (saxagliptin) therapy (Pech, Abusaada, & Alemany, 2015). Under saxagliptin, serotonin levels doubled as the tumor progressed. Cessation of saxagliptin reduced serotonin levels to those before the treatment onset so that this temporal correlation suggests a possible relationship between carcinoid tumor activity and the use of DPP4 inhibitors (Pech et al., 2015). A higher expression of DPP4 was also reported in dermal fibroblasts following skin wounding in mice (Arwert et al., 2012). By treatment with IL-1α of dermal fibroblasts the activity of CD26 was stimulated and it was hypothesized that epidermal IL-1α release may contribute to the upregulation of CD26 expression in wounded dermis. Also here, the pharmacological inhibition of CD26 via sitagliptin reduced tumor growth, while combined inhibition of IL-1α and CD26 delayed tumor onset and reduced tumor incidence (Arwert et al., 2012).

With regard to the value of CD26/DPP4 as a therapeutic target in human cancer, currently there is only one phase-I clinical trial, performed by Angevin and Morimoto and collaborators (Angevin et al., 2017). Before performing the trial with an anti-CD26 mAb, they tested the growth-inhibitory effect of this mAb in vitro and in vivo in a human renal carcinoma mouse xenograft model. They showed that in vitro, the anti-CD26 mAb caused internalization of cell surface CD26, cell cycle arrest and decreased cell adhesion to the extracellular matrix. In vivo, the *anti-CD26* mAb treatment drastically inhibited tumor growth (Inamoto et al., 2006). The authors subsequently developed a humanized anti-CD26 mAb (YS110, IgG1) against CD26 and tested it against mesothelioma cell lines. They convincingly demonstrated that through the modulation of various cell cycle regulating molecules, the cell cycle of these cells was delayed and tumor growth was inhibited in vivo (Hayashi et al., 2016). Using this antibody, the authors accumulated more evidence of the antitumor effect in various experimental models (Inamoto et al., 2007; Yamada et al., 2013; Yamamoto et al., 2014). Finally, researchers employed YS110 in standard therapy-resistant or refractory patients with CD26-expressing tumors (mesothelioma, renal cell and urothelial carcinoma). In this study, the antibody was not only well tolerated by these patients but also stabilized the disease in patients suffering from mesothelioma (Angevin et al., 2017).

Taken together, there is now fairly strong experimental and some clinical evidence that certain types of tumors, particularly mesothelioma, express higher levels of CD26 and are thereby targetable by DPP4 inhibitors or antibodies.

9. Conclusion

As CD26/DPP4 is widely expressed and has many substrates and interaction partners, it is currently not an easy task to determine its exact role in cancer. Combined molecular, cellular and (pre)clinical studies have greatly contributed to our understanding of the role of CD26/DPP4 as a marker or target in cancer therapy. However, there is a need for follow-up experimental and clinical studies to further elucidate its role in different tumor types.

It is clear that the role of CD26/DPP4 is diverse as its function in tumorigenesis varies depending on the tumor type, being either up- or downregulated in various cancer types. While mostly acting as a pro-oncogene, CD26/DPP4 displays an anti-oncogenic function in some tumors, which has, for example, been linked to the CXCL12-axis in glioma and prostate cancer.

It is currently not clear whether targeting the enzymatic activity with inhibitors or whether targeting the CD26/DPP4 protein itself by mAbs in $CD26^+$ tumors would be the more preferable treatment concept. In many studies using inhibitors, sitagliptin was employed. In future studies, it would be interesting to investigate whether other DPP4 inhibitors can exert similar effects.

It will be important to gain a more detailed and precise understanding of the interplay between CD26/DPP4 and the tumor microenvironment, e.g. its relation to chemokines and chemokine receptors, the exact CD26 localization in tumor cells and on immune cells. This understanding can then be the base for new treatment modalities for selected patients who may benefit the most from a given CD26/DPP4 targeted or immunotherapy in an adjuvant or even neo-adjuvant setting. It will also be important to determine whether cancer patients that have low or no CD26/DPP4 expression would also benefit from a CD26/DPP4-targeted therapy as is the case for some patients that do not express PD-L1 but that do successfully respond to checkpoint inhibitors. In the new era of precision medicine, it is likely that CD26/DPP4 targeted therapies could become part of a multi-faceted treatment regimen, e.g. in combination with a check-point inhibitor. Furthermore, it is evident that CD26/DPP4 holds promise as part of a panel of biomarkers in cancer and treatment of some cancer types. However, its functional role in cancer remains complex and more experimental and clinical studies are needed in this field.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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