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Review

CD26/dipeptidyl peptidase IV and its role in cancer

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Summary. CD26/Dipeptidyl Peptidase IV (DPPIV) is a 110-kDa glycoprotein that is expressed on numerous cell types and has multiple biological functions. A key facet of CD26/DPPIV biology is its enzymatic activity and its physical and functional interaction with other molecules. The substrates of CD26/DPPIV are proline-containing peptides and include growth factors, chemokines, neuropeptides, and vasoactive peptides. DPPIV plays an important role in immune regulation, signal transduction, and apoptosis. Furthermore, CD26 appears to play an important role in tumor progression. In the present review, we summarize key aspects of CD26/DPPIV involvement in tumor biology and its potential role in cancer development and behavior.

Key words: CD26/DPPIV, T cell lymphoid malignancies, Chemokines, Cancer, Targeted therapy

CD26/DPPIV is a multifunctional molecule

CD26/DPPIV is a 110-kDa cell surface glycoprotein that belongs to the serine protease family. It is expressed on a variety of tissues including T lymphocytes, endothelial and epithelial cells. It is composed of a short cytoplasmic domain, a transmembrane region, and an extracellular domain with dipeptidyl peptidase activity which selectively removes the N-terminal dipeptide from peptides with proline or alanine in the second position (Tanaka et al., 1992). Possible substrates of DPPIV include several critical cytokines and chemokines. Activity of RANTES (regulated on activation, normal T cell expressed and secreted) is altered by the enzymatic cleavage of DPPIV, as CD26/DPPIV enzymatic cleavage of RANTES affects important activities such as those implicated in monocyte chemotaxis and HIV-1 infection (Proost et al., 1998). Other important chemokines that appear to be substrates of the enzymatic activity of DPPIV include eotaxin, macrophage- derived chemokine (MDC), interferon inducible chemokines, and other chemokines involved with the inhibition of HIV infection (Proost et al., 1999). In addition, recent work showed that CD26 plays an important role in the mobilization of hematopoietic stem cell (HSC) and hematopoietic progenitor cells (HPC) induced by granulocyte colony-stimulating factor (G-CSF). One of the substrates of CD26/DPPIV is CXCL12, an important chemokine that serves as a chemoattractant for HSC/HPC. It has been shown that CXCL12 can be selectively truncated in vitro by CD26/DPPIV, and the truncated molecule lacks the ability to induce migration of hematopoietic cells isolated from mouse bone marrow. Furthermore, when mice were treated with CD26 inhibitors during G-CSF mobilization, a significant reduction in number of HPC mobilized was observed (Christopherson et al., 2003a,b).

Besides its ability to regulate the effect of biological factors through its enzymatic activity, CD26/DPPIV has an essential role in human T cell physiology. Originally characterized as a T-cell differentiation antigen, CD26 is preferentially expressed on a specific population of T-lymphocytes, the subset of CD4+ memory T-cells, and is up-regulated after T cell activation (Morimoto et al., 1989). Besides being a marker of T-cell activation, CD26 is also associated with T cell signal transduction processes as a costimulatory molecule (Dang et al., 1990a-c; Torimoto et al., 1992). In addition CD26 serves as a functional collagen receptor with a role in T cell activation, as well as having a potential role in thymic ontogeny (Dang et al., 1990d, 1991). The enzymatic activity of CD26 appears to be very important in enhancing cellular responses to external stimuli. For example, Jurkat cells transfected with wild type CD26 consistently demonstrated greater activation than parental CD26 negative Jurkat or cells transfected with CD26 mutated at the DPPIV enzymatic site (Tanaka et al., 1993). Furthermore, CD26 interacts with several molecules with important roles in T-cell function. CD26 interacts with CD45RO, a tyrosine phosphatase with

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critical role in T cell signal transduction, in lipid rafts in peripheral blood T lymphocytes, leading to modification of cellular signaling events (Torimoto et al., 1991; Ishii et al., 2001). Interestingly, CD26 is associated with CD45 RA outside of lipid rafts in cord blood T cells, and the strong physical linkage of CD26 and CD45 RA may be responsible for the attenuation of cord blood T-cell activation signaling through CD26, which may in turn result in immature immune response and the relatively low incidence of severe graft-versus-host disease in cord blood transplantation (Kobayashi et al., 2004). CD26 also physically binds with adenosine deaminase (ADA), an enzyme that plays a key role in the development and function of lymphoid tissues (Kameoka et al., 1993; Morrison et al., 1993; Dong et al., 1996, 1997). ADA is essential for purine metabolism and loss of ADA leads to a clinical syndrome characterized by severe immunodeficiency. It is also expressed in a variety of tissues including endothelial and epithelial cells. It is detected as a soluble form in plasma and other body fluids. When the ADA inhibitor pentostatin was used in the treatment of recurrent T cell lymphomas, a significant reduction in circulating CD26+ T lymphocytes was observed in treated patients (Dang et al., 2003a). This finding is consistent with the fact that there is a physical association between CD26 and ADA on the surface of T lymphocytes. Another molecule that binds CD26 is mannose-6-phosphate/insulin growth factor II receptor (M6P/IGFIIR) and this interaction also appears to be important in CD26-mediated-T-cell activation and T cell migration (Ikushima et al., 2000, 2002). Meanwhile, soluble CD26/DPPIV molecule upregulates expression of CD86 on antigen presenting cells (APC), leading to greater APC-T cell interaction and enhanced T cell proliferation, with important implications for immunoregulation (Ohnuma et al., 2001). An emerging facet of CD26 biology is its involvement in tumor development and behavior, which will be covered for the rest of this review paper.

CD26 and cancer

Recent work has examined DPPIV/CD26 expression across a wide spectrum of malignancies in an attempt to elucidate its potential role in tumor development. Besides the fact that CD26/DPPIV status may be altered in certain malignancies, work from multiple groups has shown that CD26 can affect growth and development of selected tumors. Of note is the fact that while CD26 absence is associated with tumor development in certain cancers, CD26 presence is linked with aggressive behavior in other tumor types. Loss or alteration of DPPIV has been observed in hepatocellular carcinoma. DPPIV activity has a typical distribution in normal liver, being localized in the bile canalicular domains of the hepatocellular membranes. In non-neoplastic diseases of the liver, such as cirrhosis and steatosis, the distribution pattern of the enzyme is maintained. Stecca et al. reported on the altered activity of DDPIV in hepatocellular carcinoma, observing loss of activity in some cases and an alteration of the typical distribution of the enzyme in other instances (Stecca et al., 1997).

CD26/DPPIV is highly expressed in normal melanocytes but not in melanoma cells. Several studies have shown that the expression of DPPIV is lost during malignant transformation and tumor progression. An earlier study by Houghton and colleagues reported that the expression of adenosine deaminase binding protein, subsequently found to be identical to CD26/DPPIV, is lost during malignant transformation of human melanocytes (Houghton et al., 1988). In a follow-up study, the same group showed that the loss of DPPIV occurred late during transformation, and was associated with the emergence of growth factor independence and the development of specific chromosome abnormalities (Morrison et al., 1993). Wesley et al. subsequently confirmed the role of DPPIV in suppressing the malignant phenotype in melanoma cells. Tetracycline-inducible expression vectors were used to transfect melanoma cell lines with DPPIV. Using three different cell lines the authors were able to select numerous clones with different DPPIV expression. Tumor growth was reduced in melanoma cells expressing DPPIV, and a relationship was observed between levels of expression and grade of inhibition. Also, the expression of DPPIV decreased the ability of melanoma cells to grow in soft agar indicating that DPPIV is important for the inhibition of anchorage-independent growth. The expression of DPPIV was associated with marked phenotypic changes. Cells expressing DPPIV showed a more organized growth and sheet-like appearance as opposed to parental melanoma cells and cells transfected with control vector. Also, expression of DPPIV was associated with a more differentiated phenotype. In terms of effect on cell growth, no change was observed in the logarithmic phase, but cells transfected with wild-type DPPIV had a longer lag period before entering the logarithmic growth phase, and the growth was inhibited when cells reached a confluent state (Wesley et al., 1999). Pethiyagoda et al confirmed that dipeptidyl peptidase IV inhibits cellular invasion of malignant melanoma cell lines. In fact, when expression of DPPIV was restored by cDNA transfection, a significant decrease in cellular invasiveness was noted (Pethiyagoda et al., 2001).

Meanwhile, DPPIV is selectively expressed in lung adenocarcinoma, whereas other subtypes were found to be DPPIV- (Asada et al., 1993). A recent study conducted by Wesley et al. suggests that DPPIV may have an important role in suppressing the growth and progression of NSCLC. The cell surface expression and enzymatic activity of DPPIV were found to be decreased in NSCLC cell lines as opposed to normal bronchial and alveolar epithelium. Furthermore, when NSCLC cells were transfected with DPPIV several changes were noted including morphologic changes, contact inhibition, and reduced ability of anchorage–independent growth. In addition, an increased percentage of cells in G0-G1

was noted in DPPIV-expressing cells indicating that DPPIV may promote cell cycle arrest (Wesley et al., 2004).

Several studies have suggested a regulatory role of this enzyme in the neoplastic transformation and progression of ovarian carcinoma. Expression of DPPIV varies in ovarian carcinoma cell lines. Kajiyama et al. reported that expression of DPPIV is negatively correlated with invasive potential, suggesting a role of DPPIV in cancer invasion. In addition, cell lines expressing DPPIV showed an epithelioid pattern as opposed to spindle/bipolar pattern observed in DPPIV-negative cell lines. When cell lines were transfected with DPPIV the same morphological changes were observed. Both invasion and migration were reduced by the transfection of DPPIV in carcinoma cell lines. Also, transfection of DPPIV resulted in decreased intraperitoneal dissemination and prolonged survival in vivo (Kajiyama et al., 2002). In a follow-up study the same authors investigated the possible interaction of DPPIV with cadherins and other molecules involved in cancer progression and metastasis. Cadherins are transmembrane glycoproteins that play a major role in cell-cell adhesion. Particularly, one of these glycoprotein, E-cadherin, appears to be important for tumor invasiveness. In this study the authors confirmed that higher DPPIV expression is correlated with less metastatic potential *in vivo*. The effect of DPPIV appears mediated through the up-regulation of other important enzymes such as E-cadherin and tissue inhibitors of matrix metalloproteinases. DPPIV expression was positively correlated with E-cadherin expression, and an upregulation of E-cadherin was observed also in transfected lines. When the expression of matrix metalloproteinase was evaluated in DPPIV-transfected cells, levels were found to be significantly lower. Conversely, tissue inhibitors of matrix metalloproteinases were up-regulated by DPPIV transfection (Kajiyama et al., 2003). Similarly, DPPIV appears to be involved in the transformation and progression of endometrial adenocarcinoma. DPPIV is expressed in normal endometrium. Khin et al. reported on the role of DPPIV in normal endometrium and endometrial adenocarcinoma of different histologic grades. DPPIV expression was found in both the proliferative and secretory phase of normal endometrium, although in the latter the expression was lower. The DPPIV expression in adenocarcinoma was strong or moderate in grade 1, whereas it was weak or negative in grades 2 and 3. There was no correlation between DPPIV expression and clinical stage (Khin et al., 2003).

CD26 also appears to have an important role in the development of selected hematological malignancies. Higher levels of CD26 are expressed on B-chronic lymphocytic leukemia cells, as opposed to the normal resting B cell counterpart. In addition, treatment of B-CLL cell with such agents as interferons and retinoic acid led to the enhancement of CD26 expression by activating Stat 1 alpha-mediated signaling processes (Bauvois et al., 1999). Meanwhile, in select subtypes of T-cell neoplasms, expression of CD26 appears to be correlated with a worse prognosis. Carbone and colleagues reported that CD26 expression is found mainly in aggressive subtypes of non-Hodgkin's lymphomas (NHL) such as T-lymphoblastic lymphoma (LBL)/T-acute lymphoblastic leukemia (ALL) and T–cell CD30+ anaplastic large cell (ALC) lymphoma. The expression of CD26 and CD40L was mutually exclusive, as CD40L was expressed on more indolent diseases. Also, the expression of CD26 in T-cell LBL/ALL was found to be associated with a significant worse survival (Carbone et al., 1994, 1995). Other work also demonstrated an enhancement in the expression of CD26/DPPIV in cases of T cell acute lymphoblastic leukemia. The majority of patients with T-ALL were found to express CD26 on the tumor cell surface, with a strong correlation noted between CD26 expression and the presence of DPPIV enzyme activity in the T-lymphoblasts (Klobusicka et al., 1999). The presence of CD26 and DPPIV activity was also detected on the surface of tumor cells from a patient with an aggressive hepatosplenic gamma-delta T-cell lymphoma (Ruiz et al., 1998). Similarly, in T-cell large granular lymphocyte leukemia (T-LGLL) the presence of CD26 is associated with a more aggressive clinical course. T-LGLL is a clonal disorder characterized by infiltration of bone marrow, liver and spleen with large granular lymphocytes (LGL) which are typically $CD3^+CD16^+CD57^+$. Patients affected with this disorder present with recurrent infection due to neutropenia, anemia, and often have autoimmune diseases. In T-LGLL, patients with CD26 positivity developed severe neutropenia, and were more likely to develop infections and to require treatment. In contrast, patients with low CD26 expression had a more indolent clinical course. Also, the presence of CD26 on the surface of T-LGLL appears to be important for the inhibition of myeloid progenitors, thus potentially explaining the association between level of expression and grade of myelosuppression (Dang et al., 2003b). On the other hand, CD26 is absent or weakly expressed in other types of T-cell lymphoma. When CD26 expression was examined in the peripheral blood of patients with Mycosis Fungoides (MF) or Sezary Syndrome, an abnormal CD 26-/dim cell population was identified (Bernengo et al., 2001; Jones et al., 2001). Loss of CD26 expression appears to be characteristic of CTCL and has been suggested as a useful marker in the diagnosis of this disease (Jones et al., 2001).

In view of CD26 involvement in T cell biology and particularly in T cell malignancies, CD26 may be an appropriate target for therapy in selected T-cell tumors. We recently demonstrated that anti-CD26 monoclonal antibody exhibits antitumor activity. Specifically, anti-CD26 monoclonal antibody inhibits the growth of the human CD30+ -anaplastic large cell T-cell lymphoma cell line Karpas 299 in *in vitro* studies. Importantly,

SCID mice that were injected with Karpas 299 cells and then treated with anti-CD26 monoclonal antibody showed significant improvement in overall survival (Ho et al., 2001). Besides the observed effect of the anti-CD26 monoclonal on tumor growth inhibition, the enzymatic activity of DPPIV appears to be important in determining the sensitivity of the neoplastic cells to cytotoxic agents. We demonstrated that the T cell leukemia cell line Jurkat transfected with wild type CD26 molecule (wtCD26) has a greater sensitivity when exposed to doxorubicin and etoposide as compared to the parental cells (Aytac et al., 2001, 2003; Sato et al. 2003; Sato and Dang, 2003). Significantly, Jurkat cells transfected with a mutated CD26 molecule with a nonfunctional DPPIV site (S630A) were similar to control parental Jurkat and did not exhibit enhanced sensitivity to doxorubicin and etoposide. Our work also elucidated the potential mechanism involved by demonstrating that CD26/DPPIV presence led to enhanced expression of the key intracellular protein topoisomerase II alpha, which is the target molecule for the topoisomerase II inhibitors doxorubicin and etoposide. These data thus indicated that the presence of CD26, particularly its enzymatic activity, can mediate enhanced sensitivity to topoisomerase II inhibitors by inducing increased expression of the target enzyme topoisomerase II alpha, findings which have a significant clinical implications for the treatment of T cell malignancies as well as potentially other cancers. In addition the association between CD26/DPPIV expression and topoisomerase II alpha, which is involved in cell growth and proliferation, may explain the clinical observation that CD26 is associated with aggressive clinical behavior in selected cancers, including T cell malignancies.

Conversely, upregulation of DPPIV has been observed in other malignancies. DPPIV enzyme activity is elevated in prostate cancer as compared to benign prostatic tissue. Wilson et al. measured the activity of DPPIV in prostate cancer and benign prostatic hyperplasia (BPH) tissues. DPPIV activity was detected in both BPH and cancer tissues, but the activity was increased to approximately twofold in cancer. Increased DPPIV activity was also found in benign hyperplastic glands adjacent to neoplastic tissues (Wilson et al. 2000). Upregulation of DPPIV has also been observed in thyroid carcinoma, whereas benign thyroid diseases are usually negative for DPPIV expression. Because of the significant difference in pattern of expression, immunohistochemical staining with DPPIV antibody has been shown to be a useful test in the differential diagnosis of thyroid tumors (Aratake et al., 1991; Kotani et al., 1991, 1992a,b; Tanaka et al., 1995; Hirai et al., 1999).

Besides its expression on tumor cell surface, CD26 can also be found in the serum, and its levels are correlated with disease status and tumor behavior for certain cancers. In colorectal cancer, serum CD26 levels may have potential diagnostic and prognostic value (Cordero et al., 2000). Patients with colorectal cancer have lower levels of serum CD26 than normal donors. Preoperative serum CD26 level is a distinct variable with greater diagnostic efficiency than that demonstrated by other markers, particularly in patients with early stage disease, as high preoperative serum CD26 levels were significantly associated with worse disease-free status in patients with early-stage colorectal cancer. A significant decrease in serum DPPIV activity has been reported in patients with oral cancers as compared to healthy subjects. The decreased serum activity observed in oral cancer patients appears to be correlated with a decreased enzymatic activity and CD26 expression in the plasma membrane of peripheral blood T lymphocytes (Uetmasu et al, 1996, 1998).

CD26/DPPIV may also have a role in tumor migration and metastasis due to its ability to bind extracellular matrix proteins. Several groups have demonstrated that CD26 binds to collagen and fibronectin in a variety of experimental conditions (Dang et al., 1990d; Bauvois et al., 1988; Loster et al., 1995; Piazza et al., 1989). By interacting with the extracellular matrix components, CD26 may affect immune regulation by recruiting activated lymphoid cells to sites of inflammation or tumor (Masuyama et al., 1992). Moreover, the ability of CD26 to interact with the extracellular matrix can influence the biology and clinical behavior of tumors. CD26 molecules found on lung endothelial cells specifically bind to fibronectin found on breast cancer cell surface, promoting tumor adhesion and matastasis (Cheng et al., 1998). This CD26-fibronectin interaction inhibits tumor metastasis in animal models, findings with important clinical implications (Abdel-Ghany et al., 1998). Meanwhile recent work has identified the CD26/DPPIV binding site on fibronectin, and peptides containing this CD26/DPPIV-binding domain of fibronectin blocked the interaction between CD26/DPPIV-fibronectin and significantly decreased pulmonary metastasis of tumor cells (Cheng et al., 2003).

In this review, we have discussed key aspects of CD26/DPPIV, particularly its involvement in the development and progression of different malignancies. While other aspects of CD26 biology are better elucidated, the role of CD26/DPPIV in tumor biology and development is an important and emerging facet of this multifunctional molecule. While CD26/DPPIV expression seems to be associated with decreased cancer progression in certain cancers, in others upregulation of CD26 is associated with a more aggressive clinical course. This seemingly contrasting effect of CD26/DPPIV in different tumor types can be probably explained in part by the multifunctional nature of this molecule. Thus, CD26/DPPIV could exert different functions depending on the specific mechanisms and molecules involved in tumor development and progression. In addition, its DPPIV enzymatic activity is capable of degrading multiple chemokines, which likely have different effect on tumor growth in a variety of

neoplasms. Moreover, binding of CD26/DPPIV to extracellular matrix proteins can influence tumor growth by regulating tumor adhesion, migration, and metastasis. Given the multiple functions of CD26 and its potential involvement in tumor biology, the development of therapeutic modalities targeting this fascinating molecule may indeed prove to be a useful strategy in the treatment of selected tumors.

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