

Gene Section

Review

DPP4 (dipeptidyl-peptidase 4)

Kei Ohnuma, Chikao Morimoto

Department of Therapy Development and Innovation for Immune disorders and Cancers, Graduate School of Medicine, Juntendo University, 2-1-1, Hongo, Bunkyo-ku, Tokyo 113-8421, Japan (KO, CM)

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Identity

Other names: ADABP, ADCP2, CD26, DPPIV, TP103

HGNC (Hugo): DPP4

Location: 2q24.2

DNA/RNA

Note

In 1979, a large molecular weight complex composed of adenosine deaminase (ADA) were reported to be found as an adenosine deaminase-binding protein (ADBP), also known as adenosine deaminase complexing protein-2 (ADCP2). In 1993, this adenosine deaminase-binding protein is determined to be identical to CD26, a T-cell activation molecule and a 110-kD glycoprotein that is present also on epithelial cells of various tissues including the liver, kidney, and intestine. The CD26 cDNA contains a 3465 bp open reading frame that encodes a 766 amino acid protein. The CD26 amino acid sequence has 85% amino acid identity with the

mouse and rat CD26 genes and 37% amino acid identity with *D. melanogaster*.

Two CD26 transcripts (4,2 and 2,8 kb) were found, both of which were expressed at high levels in the placenta and kidney and at moderate levels in the lung and liver. However, only the 4,2 kb mRNA was expressed at low levels in skeletal muscle, heart, brain, and pancreas.

Transcription

The 5'-flanking region does not contain a TATA box or CAAT box, commonly found in housekeeping genes. CD26 does contain a 300 base-pair G-C rich region with potential binding sites for NF- κ B, AP2, or Sp1. CD26 expression is activated by interferons (IFNs) and retinoic acid in chronic lymphocytic leukemia (CLL) via Stat1 α and the GAS response element (TTCnnnGAA located at bp -35 to -27) in the CD26 promoter. A hepatocyte nuclear factor 1 binding site at position -150 to -131 of the CD26 gene regulates CD26 expression in human intestinal (Caco-2) and hepatic epithelial (HepG2) cell lines.



Location of DPP4 gene on chromosome 2q24.3. DPP4 spans 82,301 kbp of chromosome 2 from 162848751 to 162931052. The gene contains 26 exons (indicated in orange squares), ranging from 45 to 1,4 kb in length on the reverse strand. The Ser recognition site (G-W-S-Y-G) is split between exons 21 and 22.



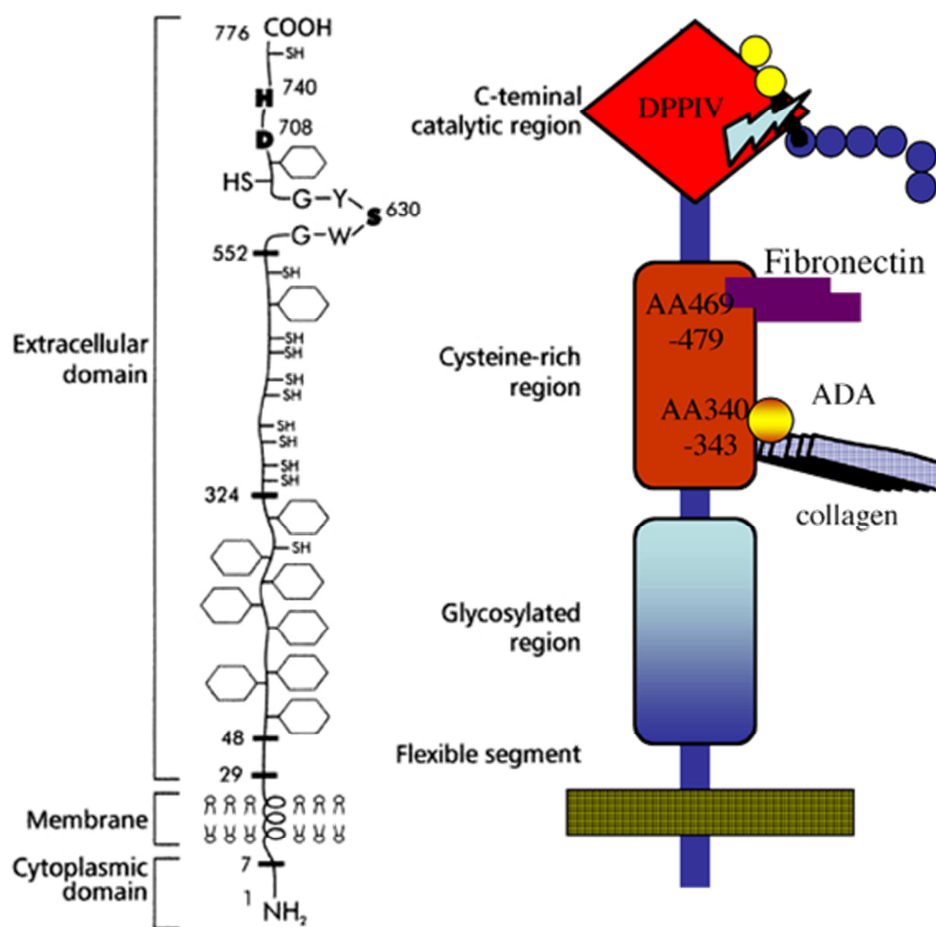
The schematic diagrams of the amino acids of DPP4. The cDNA of DPP4 is composed of 2301 base pairs, translated to 766 amino acid protein. CD26/DPP4 is a ubiquitous, membrane-bound enzyme that has roles in nutrition, metabolism, the immune and endocrine systems, bone marrow mobilization, cancer growth and cell adhesion. DPP4 catalyzes the hydrolysis of N-terminal dipeptides from polypeptides with proline or alanine in the penultimate position. Note: residues 1-6: cytoplasmic domain (MKTPWK); residues 7-29: transmembrane domain (VLLGLLGAAALVTI ITVPVLLN); residues 30-48: flexible stalk (KGTDDATADSRKTYTLTDY); residues 201-211 and Ser603: caveolin-1 binding site (WVYEEVFSAY); residues 340-343: ADA binding site (LVAR); residues 469-479: fibronectin binding site (QLRCSGPGPL); red *: essential for DPP4 activity (Glu205, Glu206 and Tyr547); green underlined GWSYG: serine recognition site; black *: Ser630, Asp708, His740 active site triad; red boxes: odd numbered exons; green boxes: glycosylation sites; yellow box (His750): required for homodimer formation; white square at residue 492: non-synonymous cSNP (Arg492Lys); white triangle at residues 633: mutation results in retention and degradation of mutant protein in the endoplasmic reticulum (Gly633Arg).

Protein

Note

CD26 is a multifunctional type II transmembrane serine peptidase that has an extracellular domain with DPP4 enzymatic activity and a short cytoplasmic domain. It interacts with extracellular molecules and is also involved in intracellular signal transduction cascades. CD26 is important in immunology, autoimmunity, HIV, diabetes, and cancer. Interacting directly with various other cell surface and intracellular molecules, CD26 can regulate receptor specificity via its DPP4

activity and the function of various chemokines and cytokines. CD26 is expressed at low density on resting T cells, but is upregulated with T cell activation. Therefore, CD26 may have an important functional role in T-cells and overall immune function. CD26 associates with other important immunologic cell surface receptors such as CD45, CD9 and CXCR4. The multifunctional activities of CD26 are dependent on cell type and intracellular or extracellular conditions that influence its role as a proteolytic enzyme, cell surface receptor, costimulatory interacting protein and signal transduction mediator; as well as its role in adhesion and apoptosis.



Schematic representation of CD26/DPPIV. Human CD26 is composed of 766 amino acids, including a short cytoplasmic domain of 6 amino acids, a transmembrane region of 24 amino acids, and an extracellular domain with dipeptidyl peptidase activity which selectively removes the N-terminal dipeptide from peptides with proline or alanine at the penultimate position. Single amino acid point mutation in the β -propeller motif identified Glu205 and Glu206 as essential for DPPIV enzyme activity, and the central tunnel and α/β -hydrolase domains both participate in DPPIV inhibitor binding. Single amino acid point mutation at His750 residue is responsible for dimerization.

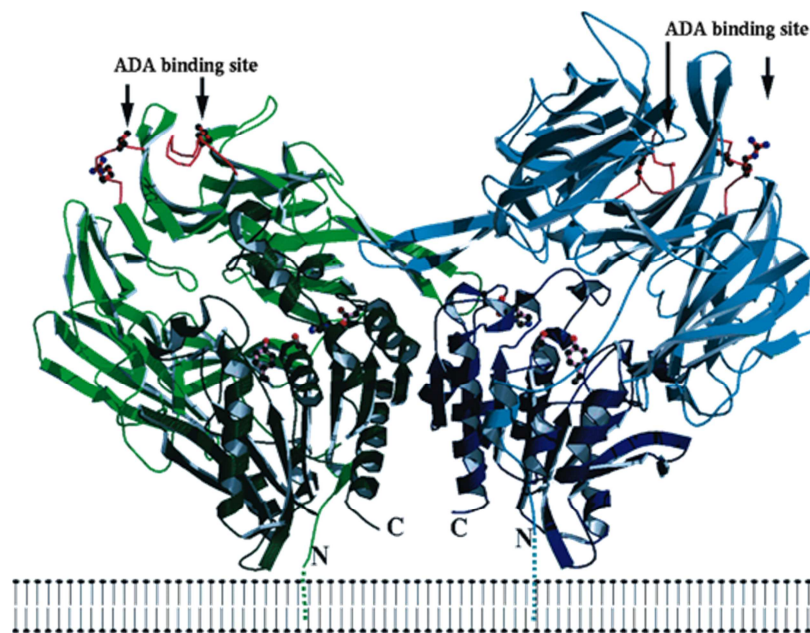
Description

Originally characterized as a T cell differentiation antigen, CD26 is preferentially expressed on a specific population of T lymphocytes, the subset of CD4⁺CD45RO⁺ memory T cells, and is upregulated following T cell activation. Besides being a marker of T cell activation, CD26 is also associated with T cell signal transduction processes as a costimulatory molecule. Recent work also suggests that CD26 has a significant role in tumor biology, being both a marker of disease behavior clinically as well as playing an important role in tumor pathogenesis and development. For instance, the association of CD26/DPPIV with such key molecules as topoisomerase II α , p38 MAPK, and integrin β 1, has important clinical implications, including its potential ability to regulate tumor sensitivity to selected chemotherapies and to influence tumor migration/metastases and tumorigenesis. DPPIV inhibitors enhance the effects of incretin hormones (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)), increasing glucose-mediated insulin secretion and suppressing

glucagon secretion. Therefore, DPPIV inhibitors, which act by inhibiting DPPIV, the enzyme that inactivates GLP-1 and GIP have been available as a new class of antidiabetes drugs.

Expression

CD26 is expressed in many tissues. Two CD26 transcripts (4,2 and 2,8 kb) are reported to be found, both of which were expressed at high levels in the placenta and kidney and at moderate levels in the lung and liver. The 4,2 kb transcript was expressed at low levels in skeletal muscle, heart, brain, and pancreas. Other organs expressing CD26 include: brain, endothelium, heart, intestine (colon adenocarcinoma, fetal colon expression disappears at birth), kidney, liver, lung, skeletal muscle, pancreas, and placenta. In the hematopoietic system CD26 is found on CD4⁺ T memory cells, CD8⁺ effector/memory T cells. It has been reported that 0-5% of freshly isolated CD20⁺ B cells do express the CD26 antigen. Following stimulation with PMA (phorbol 12-Myristate 13-acetate) or Streptococcus aureus protein, the fraction of CD26-positive cells increased to 51%.



3-D structure of CD26/DPPIV. CD26/DPPIV forms a homodimer in the cell surface membrane. The residues 7-28 constitute the membrane spanning region. Each subunit consists of two domains, that is, an α/β -hydrolase domain and a β -propeller domain. The N-terminal β -propeller domain of CD26/DPPIV (residues 55-497) consists of 8 blades. β -strand 2 of blade 4 of the propeller extends into a small domain (residues 234-260) that includes an antiparallel two-stranded β -sheet. The function of this arm is to stabilize the dimeric structure. The catalytic site (Ser630-Asp708-His740) is located in a large cavity (also called a central tunnel), formed between the α/β -hydrolase domain and 8-bladed β -propeller domain, which contains the consensus sequence (DW(V/L)YEEE), that is common to S9b proteases. The central tunnel and α/β -hydrolase domains both participate in inhibitor binding. This figure is reproduced from Ralf Thoma et al., Structural Basis of Proline-Specific Exopeptidase Activity as Observed in Human Dipeptidyl Peptidase-IV, Structure 2003;8:947-959, with permission by Elsevier Limited.

Meanwhile, CD26 is not expressed or is found only at low levels on monocytes of healthy adult. Flow cytometric analysis of dendritic antigen-presenting cells (DC) generated from peripheral blood of normal donors in the presence of granulocyte/macrophage colony-stimulating factor and revealed intermediate levels of CD26 expression during a 2-week culture period. Only a small fraction of peripheral NK cells was found to express CD26.

Localisation

CD26 physically binds with ADA, an enzyme that plays a key role in the development and function of lymphoid tissues. ADA is essential for purine metabolism, with the loss of ADA leading to a clinical syndrome characterized by severe immunodeficiency. When the ADA inhibitor pentostatin was used in the treatment of recurrent T cell lymphomas, a significant reduction in circulating CD26⁺ T cells was observed in treated patients. This finding is consistent with the fact that there is a physical association between CD26 and ADA on the surface of T lymphocytes. CD26 also interacts with CD45RO, a tyrosine phosphatase with a critical role in T cell signal transduction, at lipid rafts in peripheral blood T lymphocytes to modify cellular signaling events. A lipid raft is a cholesterol-rich microdomain in cell membrane, which plays an important role in signal transduction in T-cell regulation. CD26 interaction with lipid rafts in

peripheral blood T-cells influences key cellular signaling events. Non-activated peripheral blood T-cells treated with the anti-CD26 mAb 1F7 increased CD26 recruitment to lipid rafts, resulting in increased tyrosine phosphorylation of c-Cbl, Zap70, Erk1/Erk2, p56^{lck}, and TCR- ζ . 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. In addition to cell surface expression, nuclear localization of CD26 has been reported in malignant mesothelioma and malignant T cell lines, and in human thyroid carcinomas, although little is known on the functional relevance of nuclear CD26. In addition to membrane bound CD26, soluble form of CD26 (sCD26) is also detected in the sera, urine, thoracic fluid and seminal fluid. sCD26 in the sera appears to be functioned as immune enhancing protein in antigen-presenting cell (APC).

Function

CD26 is a co-stimulatory molecule for T-cell signal transduction. While CD26 expression is enhanced following activation of resting T cells, CD4⁺CD26^{high} T cells respond maximally to recall antigens such as tetanus toxoid. Moreover, we have previously reported that effector CD26-mediated costimulatory activity is exerted via its DPPIV enzymatic activity.

	Substrates	Biological effect	Note
Hormones	GLP-1	Inactivation	
	GLP-2	Inactivation	
	GIP	Inactivation	
	Glucagon	Inactivation	
	GHRH	Inactivation	Growth hormone releasing hormone
	PACAP	Inactivation	Pituitary adenylate cyclase-activating polypeptide
	Petide YY	Change in receptor preference	
Vasoactive peptides	Bradykinin	Change in receptor preference	
	VIP	Inactivation	Vasoactive intestinal peptide
	BNP	Change in receptor preference or Inactivation	Brain natriuretic peptide
Neuropeptides	NPY	Change in receptor preference	Neuropeptide Y
	β -casomorphins	Inactivation	
	Endomorphins	Change in receptor preference	
	Substance P	Inactivation	
Chemokines	CCL3 (MIP-1 α)	Enhanced activity	Macrophage inflammatory protein-1 α
	CCL4 (MIP-1 β)	Change in receptor preference	Macrophage inflammatory protein-1 β
	CCL5 (RANTES)	Change in receptor preference	Regulated and normal T cell expressed and secreted
	CCL11 (Eotaxin)	Inactivation	
	CCL22 (MDC)	Change in receptor preference	Macrophage-derived chemokine
	CXCL6 (GCP-2)	No changes	Granulocyte chemotactic protein-2
	CXCL9 (MIG)	Inactivation	Monokine induced by gamma interferon
	CXCL10 (IP-10)	Inactivation, CXCR3 antagonist	Interferon gamma-induced protein 10
	CXCL11 (I-TAC)	Inactivation, CXCR3 antagonist	Interferon-inducible T-cell alpha chemoattractant
	CXCL12 (SDF-1 α)	Inactivation, CXCR4 antagonist	Stromal cell-derived factor-1 α

Table 1.

In addition, CD4⁺ T cells with in vitro transendothelial migratory capacity appear to express high CD26, indicating a role for CD26 in the migration of T cells, and patients with autoimmune diseases such as multiple sclerosis, Grave's disease, and rheumatoid arthritis (RA) have been found to have increased numbers of CD4⁺CD26⁺ T cells in inflamed tissues as well as in their peripheral blood, with enhancement of CD26 expression in these autoimmune diseases correlating with disease severity. Moreover, CD26^{high}CD8⁺ T cells in humans belong to early effector memory T cells, and CD26^{high}CD8⁺ T cells increase expression of granzyme B, TNF- α (tumor necrosis factor- α), IFN- γ and Fas ligand, and exert cytotoxic effect with CD26-mediated costimulation. CD26 binds to caveolin-1 on APC, and residues 201 to 211 of CD26 along with the serine catalytic site at residue 630, which constitute a pocket structure of CD26/DPPIV, contribute to binding to the caveolin-1 scaffolding domain. This region in CD26 contains a caveolin-binding domain (Φ X Φ XXXX Φ XX Φ ; Φ and X depict aromatic residue and any amino acid, respectively), specifically WVYEEEVFSAY in CD26. These observations strongly support the notion that DPPIV enzyme activity

is necessary to exert T-cell costimulatory activation via CD26 as demonstrated in our previous report using CD26 specific mAbs. The cytoplasmic tail of CD26 is responsible for T-cell costimulation induced by anti-CD3 plus caveolin-1. It has been identified that CARMA1 binds to the cytoplasmic tail of dimeric CD26, and that a PDZ domain in CARMA1 is necessary for binding to CD26. Following its phosphorylation, CARMA1 functions as a signaling intermediate downstream of PKC θ and upstream of IKK in the TCR signaling transduction pathway leading to NF- κ B activation. Dimeric CD26, but not monomeric CD26, binds to CARMA1. The enzymatic pocket structure of the DPPIV catalytic site is necessary for binding of CD26 to caveolin-1, leading to the upregulation of CD86 expression on APC. Therefore, dimerization of CD26 is not only necessary for binding to caveolin-1, but also serves as a scaffolding structure for the cytoplasmic signaling molecule CARMA1. Overall, CD26 ligation by caveolin-1 on APC recruits CD26-interacting CARMA1 to lipid rafts, resulting in the formation of a CARMA1-Bcl10-MALT1-IKK complex, and this

membrane-associated Bcl10 complex then activates IKK through ubiquitination of NEMO.

DPPIV inactivates incretin hormone (glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP)). Therefore, DPPIV inhibitors enhance the effects of GLP-1 and GIP, increasing glucose-mediated insulin secretion and suppressing glucagon secretion.

In this regard, DPPIV inhibitors are now available worldwide for use of an antidiabetic drug. Moreover, DPPIV cleaves many cytokines and chemokines, which are summarized in Table 1.

Morimoto et al. showed that proinflammatory cytokines such as TNF- α or IL-1 β reduce expression of CD26 in microvascular endothelial cells, and that genetical or pharmacological inhibition of CD26/DPPIV enhances endothelial growth both in vitro and in vivo.

These data strongly suggest that this effect of DPP-4 inhibition on endothelial growth may be of potential use in treating diabetic vascular complications, as well as diabetes itself.

Homology

CD26/DPPIV molecule is involved in DPPIV activity and/or structure homologues (DASH), comprising seprase, fibroblast activation protein α (FAP- α), DPP6, DPP8, DPP9, attractin, N-acetylated- α -linked-acidic dipeptidase I, N-acetylated- α -linked-acidic dipeptidase II and N-acetylated- α -linked-acidic dipeptidase L, quiescent cell proline dipeptidase, thymus-specific serine protease and DPPIV- β .

Mutations

Note

Several polymorphisms in the CD26/DPPIV gene coding region have been deposited in the National Center for Biotechnology Information single nucleotide polymorphism (SNP) database (NCBI). The functional significance of coding region SNPs (cSNPs), non-cSNPs, or other polymorphisms has not been determined.

Synonymous (non-amino acid changing) polymorphisms include the following (N.D. indicates not determined):

Leu8 (T->C, exon 2, frequency: N.D.), Ile405 (C->T, exon 14, frequency: heterozygosity 0.056), Gly645 (C->T, exon 22, frequency: N.D.), Tyr661 (C->T, exon 22, frequency: N.D.).

The non-synonymous cSNP Arg492Lys (G->A, exon 18, frequency: N.D.) functional significance has not yet been determined.

CD26 experimental mutations include:

- Glu205 and Glu206 mutants (DPPIV negative activity)
- Leu294, Leu340, Val341, Ala342, Arg343, Thr440, and Lys441 mutants (ADA binding)
- Ser630Ala (DPPIV negative activity)

- Gly633Arg (retention and degradation of mutant protein in the endoplasmic reticulum)
- His750Glu (stable dimerization).

Implicated in

Adult T-cell leukemia/lymphoma

Note

A study of the human T-lymphotropic virus 1 (HTLV-1) related cancer adult T-cell leukemia/lymphoma (ATLL) showed a reduction of surface CD26 expression in the peripheral blood mononuclear cells.

Additionally, CD26 mRNA was undetectable in 7 of 8 ATLL patients. Quantification of HTLV-1 viral DNA by PCR in cells from subjects with CD26-, CD26+, and 17 HTLV-1 carriers showed that the CD26- cells had a higher HTLV-1 copy number than CD26+ cells.

This suggests that HTLV-1 has tropism for CD26- cells in vivo. In a study of 49 patients with ATLL, 10 subjects that were carriers of HTLV-1, and 4 HTLV-1 infected cell lines, ATLL HTLV-1-infected cell had reduced or absent the CD26/DPPIV expression. CD26 expression decreased with the advancement of ATLL stage. This appeared to be due to progressive aberrant methylation of CpG islands in the CD26 promoter proportional to increasing ATLL stage. This was confirmed with rescue experiments with the demethylating agent, 5-azacytidine.

Non-Hodgkin's lymphoma

Note

In Non-Hodgkin's lymphoma (NHL), CD26 expression is found mainly in aggressive subtypes, such as T-lymphoblastic lymphoma (LBL)/T-acute lymphoblastic leukemia (ALL) and T-cell CD30⁺ anaplastic large cell lymphoma (ALCL). CD26 and CD40L (CD154) expression was mutually exclusive, with CD40L expressed on cells from more indolent diseases. CD26 expression in T-cell LBL/ALL was associated with a worse survival. The majority of patients with T-ALL express CD26 on the leukemic cell surface. There appears to be high CD26/DPPIV expression on T-lymphoblasts but only moderate DPPIV activity. Aldinucci et al. showed that CD26 is a marker of poor prognosis in T-cell cancer and is a predictive marker of poor response to 2'-deoxycoformycin, pentostatin. This effect was seen in vitro in CD26/ADA positive leukemia/lymphoma T-cell lines, primary CD26⁺ T-cell cancers, and normal T-cells (CD26⁺). Loss of CD26 appears to be characteristic of cutaneous T-cell lymphoma (CTCL) and has been suggested as a useful diagnostic marker.

Sezary syndrome/mycosis fungoides

Note

CD26 expression is absent or weak in other T-cell lymphomas such as mycosis fungoides (MF) and Sezary syndrome (SS).

SS is a form of CTCL involving the blood and skin. Loss of CD26 appears to be characteristic of CTCL and has been suggested as a useful diagnostic marker. Chemokines and their receptors are involved in recruitment and homing of cancer cells to tissues of several tumors including non-Hodgkin's T-cell lymphomas. SS cells express CXCR4 and the skin generates its ligand, SDF-1, which may represent a target for the main destination of SS cells metastasizing to the skin. SDF-1 (CXCL12) is normally cleaved and inactivated by DPPIV mediated activity. An abnormal CD26-negative/dim T-cell population was found in a study of 66 of 69 samples from 28 SS/MF patients. These CD26^{negative/dim} T-cells were CD26 negative in 23 patients and CD26-weakly positive in 5 patients. Sokolowska-Wojdylo and colleagues found that absence of CD26 on CLA (cutaneous lymphocyte-associated antigen)⁺ CD4⁺ T-cells was 100% sensitive for SS in 7 patients. Also, the number of CD26-negative T-cells correlated with treatments in 2 patients for over 1 year in a longitudinal study. SS patients have decreased plasma DPPIV activity. Soluble CD26 reduces the SDF-1 mediated SS cell migratory response. Inhibition of DPPIV activity in the CD26⁺ CTCL cell line Hut78 increases SDF-1-induced migration of SS cells. The SDF-1-CXCR4 interactions may mediate SS cell affinity for skin as a metastatic site via the regulatory activity of CD26.

T-large granular lymphocyte lymphoproliferative disorder

Note

CD26 expression is associated with a more aggressive clinical course in T-cell large granular lymphocyte leukemia (T-LGLL). T-LGLL patients with low expression of CD26 on T-LGLL cells had a more indolent course, while patients with high expression developed recurrent infections due to neutropenia. LGLL patients often have autoimmune diseases. CD26 expression on T-LGLL is associated with inhibition of myeloid progenitors, possibly explaining the neutropenia seen in these patients with higher levels of CD26 expression. CD26 on T-LGLL cells is unable to transmit antibody-mediated activation signals, unlike CD26 on normal T-cells, so CD26-related signaling may be aberrant in T-LGLL. In a recent report of a single institution long-term follow-up of 21 T-LGLL patients, 0 of 21 had CD26 expression.

Breast cancer

Note

Cheng et al. found that CD26 expressed on rat lung capillary endothelium mediated lung metastases of breast cancer cells by association with fibronectin. They studied the Fischer 344/CRJ rats, which have a CD26 Gly633Arg substitution, that leads to retention and degradation of the mutant protein in the endoplasmic reticulum, as a "protein knock-out" model

to characterize the previously established role of CD26 in metastasis. They found that lung metastases from the highly metastatic MTF7 rat breast cancer cell line were reduced by only 33% relative to normal Fischer 344 rats. Detailed immunohistochemical experiments revealed low levels of mutant enzymatically inactive CD26 on lung endothelial cells. When the mutant CD26 was purified, it had identical adhesion qualities for breast cancer cells as wild type DPPIV. The CD26/fibronectin-mediated adhesion and metastasis are effectively competed by soluble CD26, anti-CD26 mAb 6A3, and anti-fibronectin antiserum. Furthermore, peptides containing the fibronectin CD26-binding domain blocked the CD26-fibronectin interaction and significantly decreased pulmonary metastasis of breast cancer and melanoma cell lines. The utilization of fibronectin by cancer cells and fibronectin self-association in the blood suggests that CD26/fibronectin binding may be a mechanism for lung metastasis. CD26 is associated with increased topoisomerase II α levels and tumor sensitivity to the topoisomerase II inhibitors, such as doxorubicin and etoposide. Recent studies suggest that topoisomerase II α level is a prognostic factor in breast cancer that is independent of stage, Her-2/neu status, and histological grading. Furthermore, anthracycline treatment did not reverse the negative prognostic effect of topoisomerase II α expression. Others have found, in retrospective studies that topoisomerase II α overexpression confers a higher probability of response to doxorubicin. Topoisomerase II α is currently being evaluated prospectively as a breast cancer predictive marker. The role of CD26 in breast cancer and the interaction of CD26 with topoisomerase II α is an area for future research.

Colon cancer

Note

CD26 is found on the cell surface and its level correlates with disease status and tumor biology for certain cancers. In colorectal cancer, soluble CD26 (sCD26) in the sera was not related to colon cancer grade, stage, or location. The DPPIV inhibitor PT-100 (Val-boro-Pro) improved the activity of trastuzumab in human Her2⁺ colon cancer in xenograft models. However, the anti-cancer activity of PT-100 was not changed in CD26^{-/-} mice, suggesting non-CD26 mediated activity. Cordero et al. found that the sCD26 concentration is diminished in serum of colorectal cancer patients compared to healthy donors, suggesting the potential utility of a sCD26 immunochemical detection test for early diagnosis. Pang et al. have identified a subpopulation of CD26⁺ cells uniformly present in both the primary and metastatic tumors in colorectal cancer patients with liver metastasis. Furthermore, in patients without distant metastasis at the time of presentation, the presence of CD26⁺ cells in their primary tumors predicted distant metastasis on follow-up.

Lung cancer

Note

CD26 is expressed in lung adenocarcinoma but not other subtypes of lung cancer. CD26 expression and DPPIV activity are present in normal bronchial and alveolar epithelium, but non-adenocarcinoma lung cancers lose CD26 expression. CD26 downregulation may contribute to the loss of growth control in non-small cell lung carcinoma (NSCLC) cells.

NSCLC cells transfected with CD26 develop morphologic changes, altered contact inhibition, and reduced ability for anchorage-independent growth. An increased percentage of cells in G0-G1 was noted in CD26 expressing cells, indicating CD26 may promote cell cycle arrest. Amatya and colleagues assessed the diagnostic utility of caveolin-1 (Cav-1), a ligand for CD26, which is expressed in endothelial cells, alveolar type I pneumocytes and mesothelial cells, as a novel positive marker of mesothelioma. Immunohistochemical study of 80 cases of epithelioid mesothelioma and 80 cases of lung adenocarcinoma was performed for the analysis of the expression of Cav-1 and other markers. Cav-1 expression with a membranous and/or cytoplasmic pattern was found in all of the epithelioid mesothelioma. Of these, 42 cases (52,5%) showed Cav-1 expression in >50% of tumour cells, 34 cases (42,5%) in 6-50% of tumour cells, and four cases (5,0%) in <5% of tumour cells. In contrast, only six cases (7,5%) of lung adenocarcinoma showed focal Cav-1 expression in the cytoplasm of the tumour cells. They concluded that Cav-1 is a novel immunohistochemical marker for the differentiation of epithelioid mesothelioma from lung adenocarcinoma.

Hepatocellular carcinoma

Note

In normal liver as well as cirrhotic and steatotic liver, CD26 is expressed in the bile canalicular domains of hepatocellular membranes. In hepatocellular carcinoma (HCC), CD26/DPPIV activity was lost (2/25 cases) or had altered distribution (23/25 cases). Gaetaniello and colleagues found Tyr phosphorylation of several proteins after antibody binding to CD26 in HCC cell lines. This effect was inhibited by CD45 Tyr phosphatase. They found that a protein or proteins with kinase activity were associated with CD26. CD26 protects against apoptosis in Jurkat T-cells, while in the human hepatoma PLC/PRF/5 cells CD26 antibody binding is pro-apoptotic. CD26 expression is also pro-apoptotic in HepG2 cells.

Glioma

Note

Low CD26/DPPIV activity is found in poorly differentiated gliomas and high activity is found in differentiated gliomas. Differentiated gliomas have higher levels of membrane-associated isoforms of CD26/DPPIV. Sedo and colleagues studied "DPPIV activity and or structure homologs" (DASH) in 5

glioma cell lines of varying grade. They concluded that there was "no simple correlation with the degree of malignancy of the original donor tumor or morphologic phenotype...". They did note that changes in DASH composition as detected by non-denaturing polyacrylamide gel electrophoresis may reflect changes in substrate specificity and regulate changes in glioma activity.

Prostate cancer

Note

CD26/DPPIV biochemical activity was twice as high in prostate cancer compared to benign prostate hyperplasia (BPH) tissues. CD26/DPPIV activity was also increased in BPH adjacent to cancerous prostate tissue. DPPIV activity was present in epithelial but not stromal BPH and cancer tissues. This suggests that paracrine factors produced by prostate cancer cells may modulate the local microenvironment to increase cancer growth. Johnson et al. found that lung endothelial cells with metastatic prostate cancer cells were enriched for CD26 compared to non-metastatic prostate cancer cells. However, Wesley et al. suggested that CD26 inhibits the "malignant phenotype" of prostate cancer cells by inhibiting the FGF signaling pathway. Wilson et al. examined DPPIV activities in different prostatic tissue zones and in prostatic expressed secretions in relation to the presence of cancer. They found that expressed prostate secretions in patients with cancer were higher than in men without cancer. DPPIV activities in the transitional and especially the peripheral zone biopsies were higher in cancer patients. They concluded that secreted DPPIV originates in the transitional and peripheral zones. Measuring DPPIV levels in prostate secretion or in post-digital rectal prostate examination urine may be a useful for tumor marker for prostate cancer. Gonzalez-Gronow et al. found that in addition to its ability to inhibit tumor vascularization, angiostatin 2ε may also directly block prostate cancer metastasis by binding to CD26 on the surface of the 1-LN prostate cancer cell line. CD26/DPPIV association with plasminogen may lead to signal transduction that regulates expression of MMP-9 in prostate cancer cells. CD26 inhibitors may inhibit prostate cancer by blocking a CD26/DPPIV mediated signal transduction pathway that regulates MMP-9 expression by prostate cancer cells.

Renal cancer

Note

CD26 expression has previously been noted in renal cell carcinoma, with unclear significance. CD26 has a high level of surface expression on the renal cell carcinoma cell lines Caki-1, Caki-2, VRMRC-RCW, and ACHN. Inamoto and colleagues showed that anti-CD26 monoclonal antibody inhibition of the Caki-2 cell line was associated with G1/S cell cycle arrest, enhanced kip1 ID: 116> expression, down regulation of cyclin-dependent kinase 2 (CDK2) and

dephosphorylation of retinoblastoma substrate (Rb). They also found that anti-CD26 monoclonal antibody therapy attenuated Akt activity and internalized cell surface CD26 leading to decreased CD26 binding to collagen and fibronectin. More importantly, they showed that anti-CD26 monoclonal antibodies inhibited human renal cell carcinoma cell growth in a mouse xenograft model, with prolongation of survival. These results suggest that CD26 is a good target for renal cell carcinoma.

Thyroid cancer

Note

Benign thyroid tissue is usually negative for CD26 expression, but CD26 expression has been observed in thyroid cancer. This difference has been exploited as a diagnostic marker for the differential diagnosis of benign thyroid disease versus thyroid cancer. Kholová et al. suggest that CD26 positivity is limited to well-differentiated thyroid carcinomas including papillary carcinoma and is of limited value for diagnosing follicular and oncocytic thyroid malignancies.

Melanoma

Note

CD26 is highly expressed in normal melanocytes, but not in melanoma cells, suggesting CD26 expression is lost in malignant transformation. Loss of CD26 was also associated with development of specific chromosome abnormalities. When CD26/DPPIV is expressed in melanoma cells using a tetracycline-inducible expression system, melanoma growth was suppressed in the clones of cell line expressing higher levels of CD26. CD26 expression also decreased the melanoma growth in soft agar - indicating a CD26 association with anchorage-independent growth. Also, CD26 can induce MMP-9 expression in cancer cells, which may facilitate metastasis. Pethiyagoda et al. confirmed that CD26/DPPIV inhibits invasion of malignant melanoma cell lines by transfecting CD26 into melanoma cell lines. Invasion in Matrigel was decreased by 75%. This was also true for CD26 mutant transfectants that either lacked the extracellular protease activity (Ser630Ala) or the six amino acid cytoplasmic domain - demonstrating that neither DPPIV activity or the six amino acid C-terminal domain were necessary to inhibit invasiveness. Expression of either wild-type CD26 (DPPIV positive) or mutant CD26 (DPPIV negative) rescued expression of the cell surface Ser protease FAP- α . FAP- α can form a heterodimer with CD26 and may play a role in regulating melanocyte/melanoma growth. CD26 can inactivate circulating growth hormone-releasing factor (GHRF), so decreased CD26 may result in cancer growth by increased GHRF. A recent study found no effect of IFN- α on DPPIV activity in 18 patients with high-risk melanoma.

Ovarian cancer

Note

Expression of CD26 varies in ovarian cancer cell lines. CD26 is negatively correlated with ovarian cancer invasive potential. Specifically, overexpression of CD26 in ovarian cancer leads to increased E-cadherin and tissue inhibitors of MMPs, resulting in decreased invasive potential. CD26 transfection in ovarian cancer cell lines decreased intraperitoneal dissemination and prolonged survival in vivo in mice.

Malignant mesothelioma

Note

Malignant pleural mesothelioma (MPM) is an aggressive cancer arising from the mesothelial cells lining the pleura. Morimoto et al. showed that CD26 is preferentially expressed on malignant mesothelioma cells but not on normal mesothelial cells, and suggested that membranous expression of CD26 indicates an importance in treatment of patients with MPM. More importantly, humanized anti-CD26 antibody inhibited growth of malignant mesothelioma cells and induced long term survival of tumor-transplanted SCID mice. In addition, it has been shown that cells from certain CD26-positive mesothelioma cell lines appeared to include the cancer stem cell characteristics for malignant mesothelioma in addition to CD24 and CD9-positive cells. Furthermore, Morimoto et al. showed that the CD26 molecule is expressed on the cell membrane of the epithelial and biphasic, but not the sarcomatoid, type of mesothelioma. Importantly, treatment outcome prediction study showed that CD26 membrane expression on MPM was closely correlated with disease responsiveness to chemotherapy. Meanwhile, in vitro studies showed that mesothelioma cells expressing high level of CD26 displayed high proliferative activity, and microarray analysis of CD26 knockdown and CD26-transfected mesothelioma cells showed that CD26 expression was closely linked to expression of genes contributing to cell proliferation, cell cycle regulation, drug-induced apoptotic action, and chemotherapy resistance. These data therefore strongly suggest that the CD26 molecule is a good therapeutic target for MPM and a clinically significant biomarker for the prediction of response to chemotherapy for MPM.

Gastric gastrointestinal stromal tumors

Note

In an immunohistochemical analysis of 152 patients with gastric gastrointestinal stromal tumors (GIST), CD26 expression was found to be associated with a poorer overall survival.

Rheumatoid arthritis

Note

Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease and is characterized by

progressive invasion of synovial fibroblasts into the articular cartilage and erosion of the underlying bone, followed by joint destruction. In antigen-induced arthritis mouse model, DPPIV^{-/-} mice showed more severe arthritis, and enzymatic activity levels of DPPIV in the plasma were significantly decreased in RA patients. Moreover, other investigators reported that inhibition of DPPIV and FAP increases cartilage invasion by RA synovial fibroblasts. However, CD26/DPPIV regulates biologic processes that are unrelated to its peptidase activity, e.g., cellular adhesion, cell differentiation, and activation via downstream signaling cascade. CD26⁺ T cells induce the inflammation and tissue destruction characteristic of RA by migrating to and being active in the rheumatoid synovium. Cordero et al. studied IL-12, IL-15, soluble CD26, and ADA serum levels from 35 patients with active and inactive RA as well as those of controls. Patients' sera had higher IL-12 and IL-15 levels, and the level of soluble CD26 was inversely correlated with the number of swollen joints. These findings suggest that these cytokines and CD26 are associated with the inflammation and immune activity in RA. Mavropoulos et al. found that anti-TNF- α therapy increases DPPIV activity and decreases autoantibodies to the chaperone protein Bip (GRP78) and phosphoglucose isomerase in 15 patients with RA. DPPIV inhibitors inhibit a rat model of rheumatoid arthritis in a dose-dependent manner. Ohnuma et al. described CD26⁺ T cells infiltrating the rheumatoid synovium using immunohistochemical studies. They found high expression of caveolin-1 in the rheumatoid synovium vasculature and synoviocytes. These data suggest that the CD26-caveolin-1 upregulation of CD86 on activated monocytes leads to antigen-specific T-cell activation in rheumatoid arthritis. DPPIV inhibitors may be useful for suppressing the immune system in rheumatoid arthritis and other autoimmune diseases.

Inflammatory bowel diseases

Note

Crohn's disease and ulcerative colitis are categorized as inflammatory bowel disease (IBD), being characterized by chronic remittent or progressive inflammatory conditions that may affect the entire gastrointestinal tract and the colonic mucosa, respectively, and are associated with an increased risk for colon cancer. Sera from IBD patients contain lower levels of circulating DPPIV activity, while membrane expression of CD26/DPPIV on T cells isolated from IBD patients is higher than healthy controls. These clinical observations indicate that CD26/DPPIV might play a significant role in perpetuating the inflammatory response associated with IBD.

Systemic lupus erythematosus

Note

Serum levels of soluble CD26 and its specific DPPIV

activity were significantly decreased in patients with systemic lupus erythematosus (SLE), and were inversely correlated with SLE disease activity index score, but not with clinical variables or clinical subsets of SLE.

More recently, Lam et al. reported that CD26 expression on invariant natural killer cells of SLE patients is decreased significantly than that of healthy controls.

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