Atlas of Genetics and Cytogenetics in Oncology and Haematology

Atlas of Genetics and Cytogenetics in Oncology and Haematology

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March 20th to March 22nd, 2013
Radboud University Nijmegen Medical Centre, The Netherlands

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LEUKAEMIAS
SOLID TUMOURS
CANCER PRONE DISEASES

- **ENTITIES: by CHROMOSOME**

X Y 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 Not Assigned

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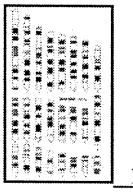

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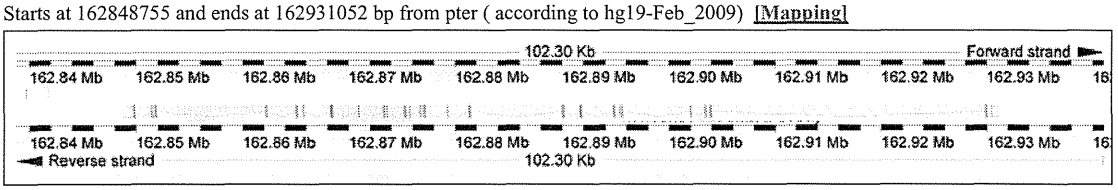
Last update : Tue Jul 3 12:44:16 CEST 2012

DPP4 (dipeptidyl-peptidase 4)

Identity

Other names	**ADABP**
	ADCP2
	CD26
	DPPIV
	TP103
HGNC (Hugo)	DPP4
LocusID (NCBI)	1803
Location	2q24.2
Location_base_pair	Starts at 162848755 and ends at 162931052 bp from pter (according to hg19-Feb_2009) [Mapping]

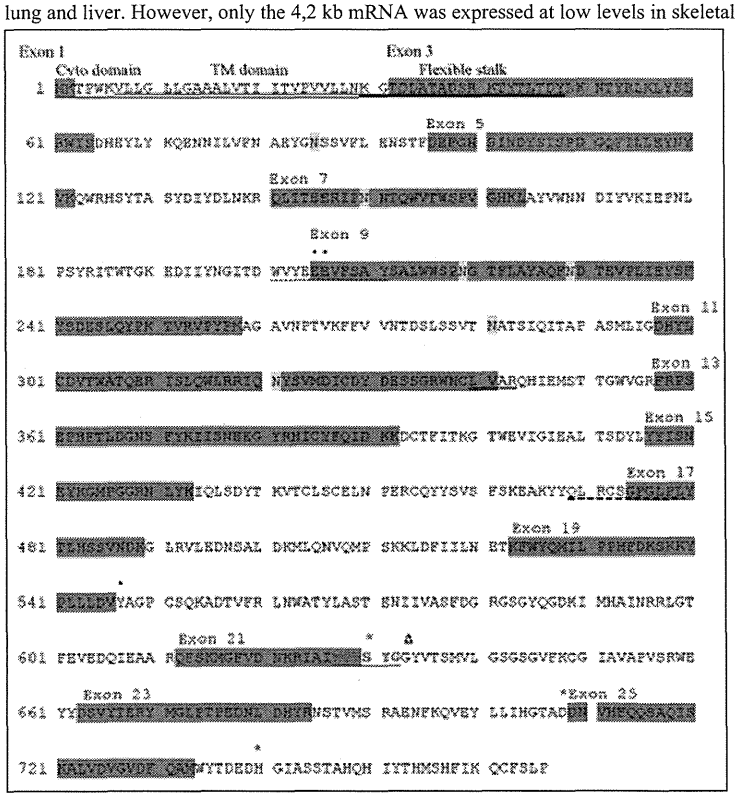


Location of DPP4 gene on chromosome 2q24.3. DPP4 spans 82,301 kbp of chromosome 2 from 162848751 to 162931052. The gene contains 26 exons (indicated in orange squares), ranging from 45 to 1,4 kb in length on the reverse strand. The Ser recognition site (G-W-S-Y-G) is split between exons 21 and 22.

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.



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. DDPIV 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 ITVPVVLLN);

residues 30-48: flexible stalk (KGTDDATADSRKTYTLTDY); residues 201-211 and Ser603: caveolin-1 binding site (WVYEEEVFSAY); residues 340-343: ADA binding site (LVAR); residues 469-479: fibronectin binding site (QLRCSGPGLPL); red *: essential for DPPIV 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).

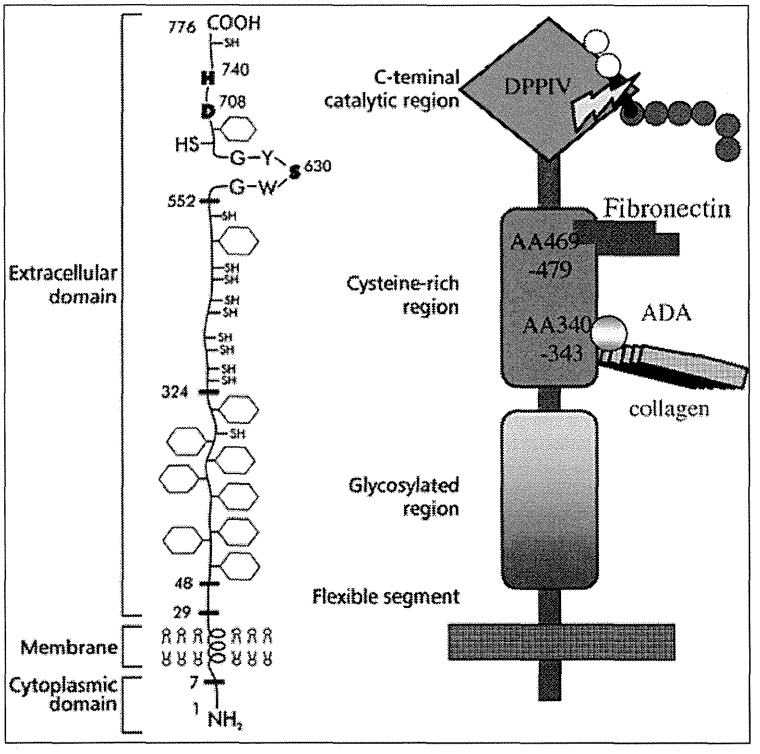
Transcription

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-κB, AP2, or Sp1. CD26 expression is activated by interferons (IFNs) and retinoic acid in chronic lymphocytic leukemia (CLL) via Stat1α 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.

Protein

Note

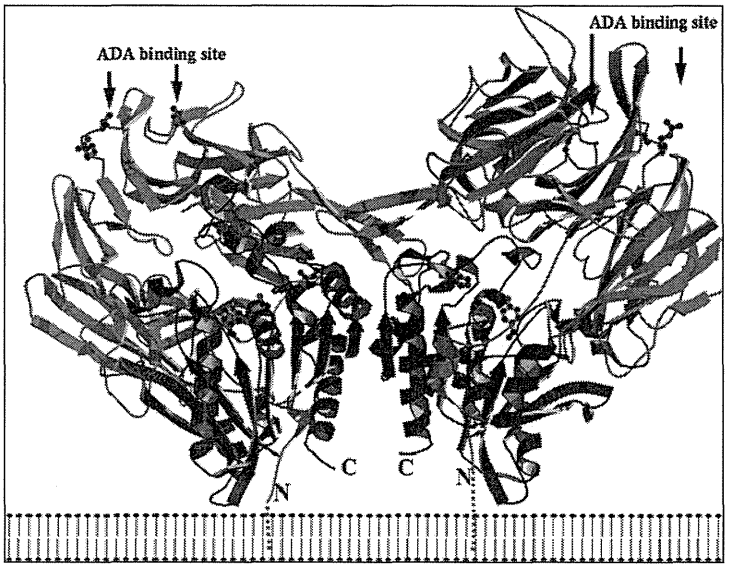
CD26 is a multifunctional type II transmembrane serine peptidase that has an extracellular domain with DPPIV enzymatic activity and a short cytoplasmic domain. It interacts with extracellular molecules and is also involved in intracellular signal transduction cascades. CD26 is important in immunology, autoimmunity, HIV, diabetes, and cancer. Interacting directly with various other cell surface and intracellular molecules, CD26 can regulate receptor specificity via its DPPIV 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 IIα, p38 MAPK, and integrin β1, 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.



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.

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%. 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 reproted that effector CD26-mediated costimulatory activity is exerted via its DPPIV enzymatic activity. 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 (ΦXΦXXXXΦXXΦ; Φ and X depict aromatic residue and any amino acid, respectively), specifically **W**V**Y**EEEV**F**SA**Y** 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 PKCθ and upstream of IKK in the TCR signaling transduction pathway leading to NF-κB 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)). Therfore, 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 avalilable worldwide for use of an antidiabetic drug. Moreover, DPPIV cleaves many cytokines and chemokines, which are summerized in Table 1. Morimoto et al. showed that proinflammatory cytokines such as TNF-α or IL-1β 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.

	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
Neuropetides	NPY	Change in receptor preference	Neuropeptide Y
	β-casomorphins	Inactivation	
	Endomorphins	Change in receptor preference	
	Substance P	Inactivation	
Chemokines	CCL3 (MIP-1α)	Enhanced activity	Macrophage inflammatory protein-1□
	CCL4 (MIP-1β)	Change in receptor preference	Macrophage inflammatory protein-1β
	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-1α)	Inactivation, CXCR4 antagonist	Stromal cell-derived factor-1α

Table 1.

Homology

CD26/DPPIV molecure 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

Entity 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-I-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.

Entity 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.

Entity 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.

Entity 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.

Entity 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 IIa levels and tumor sensitivity to the topoisomerase II inhibitors, such as doxorubicin and etoposide. Recent studies suggest that topoisomerase IIα 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 IIα expression. Others have found, in retrospective studies that topoisomerase IIα overexpression confers a higher probability of response to doxorubicin. Topoisomerase IIα 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 IIα is an area for future research.

Entity 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.

Entity 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.

Entity 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.

Entity 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.

Entity 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.

Entity 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 $p27^{kip1}$ 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.

Entity 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.

Entity 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.

Entity 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.

Entity 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 addtion, 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.

Entity 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.

Entity 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 undelying 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. Morever, 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.

Entity 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.

Entity 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.

External links

	Nomenclature
HGNC (Hugo)	DPP4 3009
Entrez_Gene (NCBI)	DPP4 1803 dipeptidyl-peptidase 4
	Cards
Atlas	**DPP4ID40360ch2q24**
GeneCards (Weizmann)	DPP4
Ensembl (Hinxton)	ENSG00000197635 [Gene_View] chr2:162848755-162931052 [Contig_View] DPP4 [Vega]
AceView (NCBI)	DPP4
Genatlas (Paris)	DPP4
SOURCE (Stanford)	NM_001935
	Genomic and cartography
GoldenPath (UCSC)	DPP4 - 2q24.2 chr2:162848755-162931052 - 2q23-qter [Description] (hg19-Feb_2009)
Ensembl	DPP4 - 2q23-qter [CytoView]
Mapping of homologs : NCBI	DPP4 [Mapview]
OMIM	102720
	Gene and transcription
Genbank (Entrez)	AB451339 AB451488 AK314798 AY429531 AY429532
RefSeq transcript (SRS)	NM_001935
RefSeq transcript (Entrez)	NM_001935
RefSeq genomic (SRS)	AC_000134 NC_000002 NC_018913 NT_005403 NW_001838860 NW_004078008

RefSeq genomic (Entrez)	AC_000134 NC_000002 NC_018913 NT_005403 NW_001838860 NW_004078008
Consensus coding sequences : CCDS (NCBI)	DPP4
Cluster EST : Unigene	Hs.368912[SRS] Hs.368912 [NCBI]
CGAP (NCI)	Hs.368912
Alternative Splicing : Fast-db (Paris)	GSHG0018103
Alternative Splicing Gallery	ENSG00000197635
Gene Expression	DPP4 [NCBI-GEO] DPP4 [EBI - ARRAY_EXPRESS]
	Protein : pattern, domain, 3D structure
UniProt/SwissProt	P27487 (SRS) P27487 (Uniprot)
NextProt	P27487
With graphics : InterPro	P27487
Splice isoforms : SwissVar	P27487(Swissvar)
Domaine pattern : Prosite (SRS)	PRO_ENDOPEP_SER (PS00708)
Domaine pattern : Prosite (Expaxy)	PRO_ENDOPEP_SER (PS00708)
Domains : Interpro (SRS)	Pept_S9_AS Peptidase_S9 Peptidase_S9B
Domains : Interpro (EBI)	Pept_S9_AS Peptidase_S9 Peptidase_S9B
Related proteins : CluSTr	P27487
Domain families : Pfam (SRS)	DPPIV_N (PF00930) Peptidase_S9 (PF00326)
Domain families : Pfam (Sanger)	DPPIV_N (PF00930) Peptidase_S9 (PF00326)
Domain families : Pfam (NCBI)	pfam00930 pfam00326
DMDM	1803
Blocks (Seattle)	P27487
PDB (SRS)	1J2E 1N1M 1NU6 1NU8 1PFQ 1R9M 1R9N 1RWQ 1TK3 1TKR 1U8E 1W1I 1WCY 1X70 2AJL 2BGN 2BGR 2BUB 2FJP 2G5P 2G5T 2G63 2HHA 2I03 2I78 2IIT 2IIV 2JID 2OAG 2OGZ 2OLE 2ONC 2OPH 2OQI 2OQV 2P8S 2QJR 2QKY 2QOE 2QT9 2QTB 2RGU 2RIP 3BJM 3C43 3C45 3CCB 3CCC 3D4L 3EIO 3F8S 3G0B 3G0C 3G0D 3G0G 3H0C 3HAB 3HAC 3KWF 3KWJ 3NOX 3O95 3O9V 3OC0 3OPM 3Q0T 3Q8W 3QBJ 3SWW 3SX4 3VJM 4A5S
PDB (PDBSum)	1J2E 1N1M 1NU6 1NU8 1PFQ 1R9M 1R9N 1RWQ 1TK3 1TKR 1U8E 1W1I 1WCY 1X70 2AJL 2BGN 2BGR 2BUB 2FJP 2G5P 2G5T 2G63 2HHA 2I03 2I78 2IIT 2IIV 2JID 2OAG 2OGZ 2OLE 2ONC 2OPH 2OQI 2OQV 2P8S 2QJR 2QKY 2QOE 2QT9 2QTB 2RGU 2RIP 3BJM 3C43 3C45 3CCB 3CCC 3D4L 3EIO 3F8S 3G0B 3G0C 3G0D 3G0G 3H0C 3HAB 3HAC 3KWF 3KWJ 3NOX 3O95 3O9V 3OC0 3OPM 3Q0T 3Q8W 3QBJ 3SWW 3SX4 3VJM 4A5S
PDB (IMB)	1J2E 1N1M 1NU6 1NU8 1PFQ 1R9M 1R9N 1RWQ 1TK3 1TKR 1U8E 1W1I 1WCY 1X70 2AJL 2BGN 2BGR 2BUB 2FJP 2G5P 2G5T 2G63 2HHA 2I03 2I78 2IIT 2IIV 2JID 2OAG 2OGZ 2OLE 2ONC 2OPH 2OQI 2OQV 2P8S 2QJR 2QKY 2QOE 2QT9 2QTB 2RGU 2RIP 3BJM 3C43 3C45 3CCB 3CCC 3D4L 3EIO 3F8S 3G0B 3G0C 3G0D 3G0G 3H0C 3HAB 3HAC 3KWF 3KWJ 3NOX 3O95 3O9V 3OC0 3OPM 3Q0T 3Q8W 3QBJ 3SWW 3SX4 3VJM 4A5S
PDB (RSDB)	1J2E 1N1M 1NU6 1NU8 1PFQ 1R9M 1R9N 1RWQ 1TK3 1TKR 1U8E 1W1I 1WCY 1X70 2AJL 2BGN 2BGR 2BUB 2FJP 2G5P 2G5T 2G63 2HHA 2I03 2I78 2IIT 2IIV 2JID 2OAG 2OGZ 2OLE 2ONC 2OPH 2OQI 2OQV 2P8S 2QJR 2QKY 2QOE 2QT9 2QTB 2RGU 2RIP 3BJM 3C43 3C45 3CCB 3CCC 3D4L 3EIO 3F8S 3G0B 3G0C 3G0D 3G0G 3H0C 3HAB 3HAC 3KWF 3KWJ 3NOX 3O95 3O9V 3OC0 3OPM 3Q0T 3Q8W 3QBJ 3SWW 3SX4 3VJM 4A5S
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HPRD	02187
IPI	IPI00018953 IPI00924974 IPI00924746 IPI00927124
	Protein Interaction databases
DIP (DOE-UCLA)	P27487
IntAct (EBI)	P27487
FunCoup	ENSG00000197635
REACTOME	DPP4
Protein Interaction Database	1803
BioGRID	DPP4
InParanoid	P27487
Interologous Interaction database	P27487
IntegromeDB	DPP4
	Polymorphism : SNP, mutations, diseases
	DPP4

SNP Single Nucleotide Polymorphism (NCBI)	
SNP (GeneSNP Utah)	DPP4
SNP : HGBase	DPP4
Genetic variants : HAPMAP	DPP4
Somatic Mutations in Cancer : COSMIC	DPP4
CONAN: Copy Number Analysis	DPP4
Mutations and Diseases : HGMD	DPP4
OMIM	102720
GENETests	102720
Disease Genetic Association	DPP4
Huge Navigator	DPP4 [HugePedia] DPP4 [HugeCancerGEM]
Genomic Variants	DPP4 DPP4 [DGVbeta]
snp3D : Map Gene to Disease	1803
	General knowledge
Homologs : HomoloGene	DPP4
Homology/Alignments : Family Browser (UCSC)	DPP4
Phylogenetic Trees/Animal Genes : TreeFam	DPP4
Catalytic activity : Enzyme	3.4.14.5 [Enzyme-Expasy] 3.4.14.5 [Enzyme-SRS] 3.4.14.5 [IntEnz-EBI] 3.4.14.5 [BRENDA] 3.4.14.5 [KEGG]
Chemical/Protein Interactions : CTD	1803
Chemical/Pharm GKB Gene	PA27467
Clinical trial	DPP4
Cancer Resource (Charite)	ENSG00000197635
Ontology : AmiGO	response to hypoxia protease binding regulation of T cell mediated immunity aminopeptidase activity serine-type endopeptidase activity receptor binding protein binding collagen binding endoplasmic reticulum Golgi apparatus plasma membrane proteolysis cell adhesion serine-type peptidase activity dipeptidyl-peptidase activity positive regulation of cell proliferation cell surface negative regulation of extracellular matrix disassembly integral to membrane apical plasma membrane lamellipodium endocytic vesicle lamellipodium membrane T cell costimulation regulation of cell-cell adhesion mediated by integrin T cell activation peptide binding protein homodimerization activity endothelial cell migration membrane raft intercellular canaliculus establishment of localization extracellular vesicular exosome invadopodium membrane
Ontology : EGO-EBI	response to hypoxia protease binding regulation of T cell mediated immunity aminopeptidase activity serine-type endopeptidase activity receptor binding protein binding collagen binding endoplasmic reticulum Golgi apparatus plasma membrane proteolysis cell adhesion serine-type peptidase activity dipeptidyl-peptidase activity positive regulation of cell proliferation cell surface negative regulation of extracellular matrix disassembly integral to membrane apical plasma membrane lamellipodium endocytic vesicle lamellipodium membrane T cell costimulation regulation of cell-cell adhesion mediated by integrin T cell activation peptide binding protein homodimerization activity endothelial cell migration membrane raft intercellular canaliculus establishment of localization extracellular vesicular exosome invadopodium membrane
	Other databases
	Probes
	Litterature
PubMed	**239 Pubmed reference(s) in Entrez**
PubGene	DPP4
iHOP	DPP4

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CD26-mediated co-stimulation in human CD8$^+$ T cells provokes effector function via pro-inflammatory cytokine production

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Summary

CD26 is an activation marker of human CD4$^+$ T cells, and is associated with T-cell signal transduction processes as a co-stimulatory molecule. We have previously demonstrated that high CD26 cell surface expression on CD4$^+$ T cells is correlated with the production of T helper type 1 cytokines, whereas CD26$^+$ T helper cells stimulate antibody synthesis in B cells. Although the cellular and molecular mechanisms involved in CD26-mediated CD4$^+$ T-cell activation have been extensively evaluated by our group and others, the role of CD26 in CD8$^+$ T cells has not been clearly elucidated. In the present study, we examine the effector function of CD8$^+$ T cells via CD26-mediated co-stimulation in comparison with CD28-mediated co-stimulation. We found that CD26^{high} CD8$^+$ T cells belong to the early effector memory T-cell subset, and that CD26-mediated co-stimulation of CD8$^+$ T cells exerts a cytotoxic effect preferentially via granzyme B, tumour necrosis factor-α, interferon-γ and Fas ligand. The effector function associated with CD26-mediated co-stimulation is enhanced compared with that obtained through CD28-mediated co-stimulation, suggesting that the CD26 co-stimulation pathway in CD8$^+$ T cells is distinct from the CD28 co-stimulation pathway. Targeting CD26 in CD8$^+$ T cells therefore has the potential to be useful in studies of immune responses to new vaccine candidates as well as innovative therapy for immune-mediated diseases.

Keywords: CD26/dipeptidyl peptidase 4; CD8; cytotoxic T-lymphocyte effect; effector memory; granzyme B.

Introduction

In addition to being a marker of T-cell activation, CD26 is associated with T-cell signal transduction processes as a co-stimulatory molecule, and the enzymatic activity of CD26 appears to play an important role in enhancing cellular responses to external stimuli.[1] Whereas CD26 expression is increased following activation of resting T cells, CD4$^+$ CD26^{high} T cells respond maximally to recall antigens such as tetanus toxoid.[2] Moreover, cross-linking of CD26 and CD3 with solid-phase immobilized monoclonal antibodies (mAbs) can induce T-cell co-stimulation and interleukin-2 (IL-2) production by CD26$^+$ T cells.[1] High CD26 cell surface expression in CD4$^+$ T cells is correlated with the production of T helper type 1 (Th1) cytokines and high migratory activity, whereas CD26$^+$ T helper cells stimulate antibody synthesis in B cells.[1] Recently, we have demonstrated that caveolin-1 is a co-stimulatory ligand for CD26 in CD4$^+$ T cells, and that CD26 on activated memory CD4$^+$ T cells interacts with caveolin-1 on tetanus toxoid-loaded monocytes.[3,4] Moreover, following CD26–caveolin-1 interaction on tetanus toxoid-loaded monocytes, caveolin-1 is phosphorylated, with linkage to nuclear factor-κB activation, followed by up-regulation of CD86, a ligand for CD28.[5,6] Taking into account the data that effector T cells in inflamed lesions express high levels of CD26, it is conceivable that CD4$^+$ CD26$^+$ T cells play an important role in the inflammatory process.

It has been recently reported that influenza-specific CD8 'memory' T cells express high levels of CD26, whereas CD8$^+$ T cells specific for chronically infecting viruses such as cytomegalovirus, Epstein–Barr virus and HIV do not express CD26.[7] This suggests that high expression of CD26 on CD8$^+$ T cells may offer a specific marker of successful memory development. More recently, it has been shown that terminally differentiated effector memory cells (CD45RA$^+$ CCR7$^-$) among

$CD8^+$ $CD26^+$ T cells are markedly increased in patients with type 1 diabetes, suggesting that the pathogenesis of type 1 diabetes might be associated with life-long stimulation by protracted antigen exposure or a homeostatic defect in the regulation/contraction of immune responses.[8]

Although the above studies analysed the phenotype of CD26-expressing $CD8^+$ T cells, more extensive research is required to fully characterize the phenotype of $CD8^+$ $CD26^+$ T cells and cellular function of $CD8^+$ T cells via CD26-mediated co-stimulation. In the present study, to explore the immunological role of CD26-expressing $CD8^+$ T cells, we examined the effector function of $CD8^+$ T cells via CD26-mediated co-stimulation in comparison with CD28-mediated co-stimulation. We found that $CD26^{high}$ $CD8^+$ T cells are among the subset of early effector memory T cells, and that CD26-mediated co-stimulation in $CD8^+$ T cells exerts cytotoxic effects preferentially via granzyme B, tumour necrosis factor-α (TNF-α), interferon-γ (IFN-γ) and Fas ligand (FasL). The effector function associated with CD26-mediated co-stimulation is enhanced in comparison with that obtained with CD28-mediated co-stimulation.

Materials and methods

Cells and antibodies

Human $CD3^+$ T cells or $CD8^+$ T cells were purified from peripheral blood mononuclear cells (PBMC) of healthy adult volunteers after their documented informed consent was obtained. This study has been performed according to the Declaration of Helsinki, and the process involved has also been approved by the institutional review board. For purification, a MACS human Pan T-cell Isolation kit or MACS human $CD8^+$ T-cell Isolation kit (Miltenyi Biotec, Bergisch Gladbach, Germany) was used. Non-$CD8^+$ T cells, namely $CD4^+$ T cells, monocytes, neutrophils, eosinophils, B cells, stem cells, dendritic cells, natural killer cells, granulocytes, $\gamma\delta$ T cells or erythroid cells were specifically depleted by using antibodies against CD4, CD15, CD16, CD19, CD34, CD36, CD56, CD123, T-cell recptor-$\gamma\delta$ and CD235a. Purity of $CD3^+$ T cells or $CD8^+$ T cells was $\geq$ 99% or $\geq$ 95%, respectively, as confirmed by FACSCalibur (BD Biosciences, San Jose, CA). No cytotoxic lymphocytes other than $CD8^+$ T cells, such as natural killer cells, were detected in the purified $CD8^+$ T-cell fraction. For cell stimulation, anti-CD3 mAb (OKT3), anti-CD28 mAb (4B10) and anti-CD26 mAb (1F7) were developed in our laboratory. Other antibodies used for flow cytometry were purchased from BD Biosciences. In experiments involving CD26-positive or negative selection, purified $CD8^+$ T cells were further separated into positively or negatively selected fractions using anti-CD26 mAb (5F8) and anti-mouse IgG_1-conjugated magnetic beads (Miltenyi Biotec). 5F8 was developed in our laboratory, and exerts no effect on $CD26^+$ T-cell function, as well as having no cross-reaction with 1F7.[9]

Detection of intracellular cytotoxic granules

Purified $CD8^+$ T cells (1×10^5) were cultured in serum-free AIM-V medium (Invitrogen, Carlsbad, CA) in 96-well flat-bottom plates (Costar, Corning Incorporated, Corning, NY), with stimulatory mAbs being bound in the wells beforehand at the following concentrations; 0·5 μg/ml of OKT3, and/or 2, 5, 10, 20 or 50 μg/ml of 4B10 or 1F7. Cells were cultured in a 5% CO_2 and 100% humidified incubator at 37° for the indicated time intervals, and cells were then prepared for analysis of intracellular perforin (PRF), granzyme A (GzmA) or granzyme B (GzmB) using a BD Cytofix/Cytoperm Plus Fixation/Permeabilization kit (BD Biosciences). The data obtained were analysed with FLOWJO software (Tree Star, Inc., Ashland, OR).

Measurement of cytokines

Purified $CD8^+$ T cells (1×10^5) were incubated with plate-bound OKT3 (0·5 μg/ml) and/or 4B10 (5 μg/ml) or 1F7 (5 μg/ml) in 96-well flat-bottom plates for 48, 72, 96 or 120 hr. After incubation, supernatants were collected and cytokine concentrations were examined using ELISA. BD OptEIA kits for human IL-2, TNF-α or IFN-γ were purchased from BD Biosciences, and a FasLigand/TNFSF6 DuoSet for soluble FasL (sFasL) was purchased from R&D Systems (Minneapolis, MN).

Quantitative real-time reverse transcription-PCR assay

Purified $CD8^+$ T cells (6×10^5) were incubated with plate-bound OKT3 (0·5 μg/ml) and/or 4B10 (5 μg/ml) or 1F7 (5 μg/ml) in 24-well flat-bottom plates (Costar) for 12, 24, 48 or 72 hr. After incubation, cells were collected and total RNA was extracted using an RNeasy Micro kit according to the manufacturer's instructions (QIAGEN, Valencia, CA). Complementary DNA was produced using a PrimeScript II 1st strand cDNA Synthesis kit (TaKaRa Bio, Shiga, Japan) with oligo-dT primer. Quantification of mRNA was performed using the 7500 Real-Time PCR System and SYBR Select Master Mix (Applied Biosystems, Foster City, CA). The data obtained were analysed with 7500 System SDS Software (Applied Biosystems), being normalized to hypoxanthine phosphoribosyltransferase (HPRT) expression. The PCR was performed using the following primers: TNF-α forward primer, 5′-TCAG CCTCTTCTCCTTCCTG-3′; reverse primer, 5′-TTTGCTA CAACATGGGCTACA-3′; IFN-γ forward primer, 5′-GTG TGGAGACCATCAAGGAAG-3′; reverse primer, 5′-ATG TATTGCTTTGCGTTGGA-3′; FasL forward primer, 5′-TG GGGATGTTTCAGCTCTTC-3′; reverse primer, 5′-TGGA

CCTTGAGTTGGACTTG-3′; IL-2 forward primer, 5′-AG AAGGCCACAGAACTGAAAC-3′; reverse primer, 5′-GCT GTCTCATCAGCATATTCAC-3′; HPRT1 forward primer, 5′-CAGTCAACAGGGGACATAAAAG-3′; reverse primer, 5′-CCTGACCAAGGAAAGCAAAG-3′.

Mixed lymphocyte reaction assay

Purified CD8$^+$ T cells (1×10^6) were incubated with plate-bound OKT3 (0·5 μg/ml) and/or 4B10 (5 μg/ml) or 1F7 (5 μg/ml) in 24-well flat-bottom plates for 72 hr. The incubated effector CD8$^+$ T cells were co-cultured in 96-well V-bottom plates (NUNC, Roskilde, Denmark) with AIM-V medium admixed with carboxyfluorescein succinimidyl ester (CFSE) -labelled U937 cells (1×10^5) as target cells. CFSE labelling of U937 cells was conducted using a Vybrant CFDASE Cell Tracer kit (Molecular Probes, Eugene, OR) according to the manufacturer's instructions. The number of target cells was fixed at 1×10^5/well in the present experiments, and effector to target (E : T) cell ratios were 1 : 1, 2 : 1, or 4 : 1. For the inhibition assays, Granzyme B Inhibitor 1 (200 μM; Calbiochem, San Diego, CA) or neutralizing anti-FasL mAb (10 μg/ml; BD Biosciences) was added to the medium for incubation at an E : T ratio of 2 : 1. After 16 hr of co-culture, cells were harvested and stained with an Annexin V-PE Apoptosis Detection kit I (BD Biosciences). CFSE-positive cells (U937 target cells) were gated in and Annexin V-positive and 7-amino-actinomycin D (7-AAD) -positive cells were detected using FACSCalibur, with data being analysed with FlowJo software.

Statistics

The paired Student's *t*-test (two-tailed) was used for the comparison of group values. The assay was performed in triplicate wells, and data are presented as mean ± SE of triplicate samples of independent experiments. Significance was analysed using MS-EXCEL (Microsoft, Redmond, WA), and values of $P < 0{\cdot}01$ were considered significant and indicated in the corresponding figures and figure legends.

Results

Human CD26^{high} CD8$^+$ T cells belong to an early effector memory subset

To characterize the phenotype of CD26-expressing CD8$^+$ T cells, we first used flow cytometry to conduct cell surface marker analysis of CD8$^+$ T cells derived from human PBMC. As shown in Fig. 1(a), CD8$^+$ T cells were divided into four subsets of CD26^{high} CD28$^+$, CD26^{int} CD28$^+$, CD26$^-$ CD28$^+$ and CD26$^-$ CD28$^-$ populations. For further examination, we performed multi-colour analysis by flow cytometry of these four populations. As shown in Fig. 1(b), CD26^{high} (exclusively CD28$^+$) CD8$^+$ T cells were enriched in the CD45RA$^-$ CCR7$^-$ population (82·3 ± 1·7%, $n = 5$) (Fig. 1b-i), whereas CD26^{int} (exclusively CD28$^+$) CD8$^+$ T cells were enriched in the CD45RA$^+$ CCR7$^+$ population (78·2 ± 2·8%, $n = 5$) (Fig. 1b-ii). Moreover, CD26$^-$ CD28$^+$ or CD26$^-$ CD28$^-$ CD8$^+$ T cells were enriched in CD45RA$^-$ and CD45RA$^+$ CCR7$^-$ (62·5 ± 5·9% and 24·7 ± 2·0%,

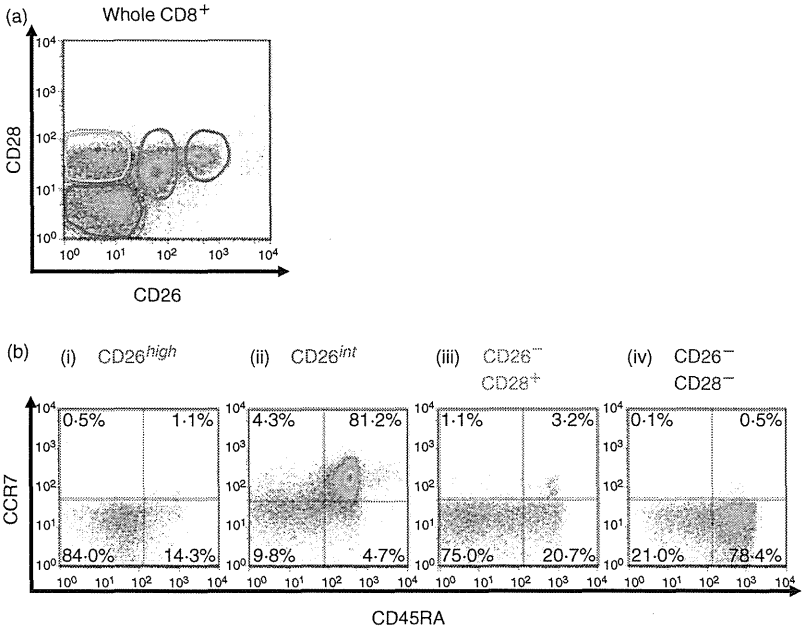

Figure 1. CD26^{high} CD8$^+$ T cells are an effector memory subset, as characterized by cell surface marker analysis. Purified CD8$^+$ T cells from peripheral blood mononuclear cells were stained with CD26, CD28, CD45RA, and CCR7 monoclonal antibodies. Cells were then analysed by multi-colour flow cytometry. (a) Two-dimensional (2D) dot blot of CD26 or CD28 staining gated for CD8$^+$ T cells, showing a representative plot of five independent donors. (b) 2D-dot blot of CD45RA or CCR7 staining gated for CD26^{high}, CD26^{int}, CD26$^-$ CD28$^+$ or CD26$^-$ CD28$^-$ cells among CD8$^+$ T cells, showing a representative plot of five independent donors.

respectively, $n = 4$) (Fig. 1b-iii), or $CD45RA^+$ $CCR7^-$ population ($71{\cdot}7 \pm 4{\cdot}9\%$, $n = 4$) (Fig. 1b-iv), respectively. These data indicate that $CD26^{high}$ $CD8^+$ T cells are effector memory (EM) cells and that $CD26^{int}$ $CD8^+$ T cells are naive cells.[10]

For further confirmation, we analysed the expression pattern of cytotoxic granules in $CD8^+$ T cells through flow cytometry. Whole $CD8^+$ T cells of human PBMC showed a triphasic pattern of expression for PRF (Fig. 2a-i), and a biphasic pattern of expression for GzmA (Fig. 2a-ii) or GzmB (Fig. 2a-iii), suggesting the presence of heterogeneous populations. Compared with the analysis of cell surface markers of $CD8^+$ T cells, as shown in Fig. 1, we analysed expression levels of PRF, GzmA or GzmB among $CD26^{high}$ $CD8^+$ (exclusively $CD28^+$), $CD26^{int}$ $CD8^+$ (exclusively $CD28^+$), $CD26^-$ $CD28^+$ $CD8^+$, or $CD26^-$ $CD28^-$ $CD8^+$ subsets. $CD26^{high}$ $CD8^+$ T cells were PRF^{int} $GzmA^+$ $GzmB^{low/-}$ (Fig. 2b-i–iii), whereas $CD26^{int}$ $CD8^+$ T cells were PRF^- $GzmA^-$ $GzmB^{low/-}$ (Fig. 2c-i–iii). These data indicate that $CD26^{high}$ $CD8^+$ T cells are an early EM subset and that $CD26^{int}$ $CD8^+$ T cells are a naive or central memory subset.[11] On the other hand, $CD26^-$ $CD28^+$ $CD8^+$ T cells were composed of PRF^{int} or PRF^-, $GzmA^+$ or $GzmA^-$, and $GzmB^{high}$ or $GzmB^{low/-}$ populations (Fig. 2d-i–iii). These data indicate that $CD26^-$ $CD28^+$ $CD8^+$ T cells are collective populations rather than a terminally differentiated effector memory (TEMRA) subset.[11] In contrast, $CD26^-$ $CD28^-$ $CD8^+$ T cells contained PRF^{high} or PRF^{int}, $GzmA^+$ and $GzmB^{high}$ populations (Fig. 2e-i–iii), indicative of TEMRA and late EM subsets.[11]

Taken together, these data indicate that $CD26^{high}$ $CD8^+$ T cells are an early EM subset and $CD26^{int}$ $CD8^+$ T cells are a naive subset, whereas $CD28^+$ $CD8^+$ T cells are composed of heterogeneous subsets. Therefore, these findings strongly suggest that $CD26^+$ $CD8^+$ T cells may have an effector function that is different from that of the $CD28^+$ subset of $CD8^+$ T cells.

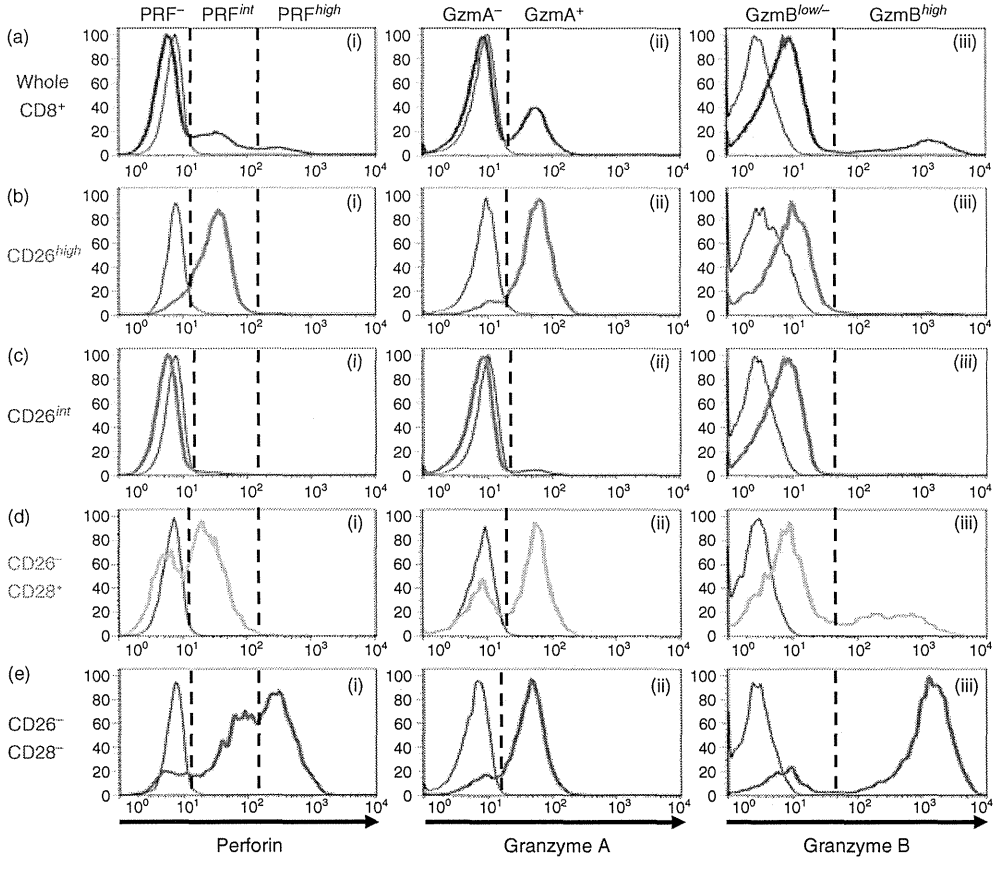

Figure 2. $CD26^{high}$ $CD8^+$ T cells are an early effector memory subset, as characterized by analysis of intracellular cytotoxic granules. Purified $CD8^+$ T cells from peripheral blood mononuclear cells were stained with CD26, CD28, perforin (PRF), granzyme A (GzmA) and granzyme B (GzmB) monoclonal antibodies, and analysed by flow cytometry. Following gating for whole $CD8^+$ population (brown lines in a), $CD8^+$ $CD26^{high}$ population (red lines in b), $CD8^+$ $CD26^{int}$ population (green lines in c), $CD8^+$ $CD26^-$ $CD28^+$ population (blue lines in d), or $CD8^+$ $CD26^-$ $CD28^-$ population (purple lines in e), each subset was analysed for the expression of PRF, GzmA or GzmB. The data are shown as histograms of PRF (i), GzmA (ii), or GzmB (iii) intensity among each subset, representative of eight independent donors. The black lines in each histogram show the data of isotype control.

