えい防止を徹底し、プライバシーの保護に努める。さらに個人に帰属する結果を個人に求められた場合には、その個人本人のもののみ伝達する旨である。

なお、フランスで実施されているヒト化CD26 抗体投与の第 I 相臨床試験における対象症例血清中の可溶性 CD26 及び DPPIV 活性の測定及びコントロール症例の可溶性 CD26 及び DPPIV 酵素活性の測定については順天堂大学の倫理審査委員会の審査にて承認されている（順天医倫第 2012076 及び 2012081）。検体の使用は患者の同意が得られているかあるいは岡山労災病院、山口宇部医療センターの臨床研究審査委員会で承認を得て研究内容について院内掲示などで周知を図った。

解析は匿名化したデータで行い個人のプライバシーが漏れることのないように配慮した。

C. 研究結果

1) 従来の ELISA 法を用いたヒト化 CD26 抗体添加による可溶性 CD26 及び DPPIV 酵素値

我々が確立した従来の可溶性 CD26 及び DPPIV 酵素値測定 ELISA 法は 5F8 抗体を固相化し、その後血清を加え、可溶性 CD26 をプレート上に捕捉し、その後可溶性 CD26 の測定はビオチンラベルした 1F7 抗体を加え、更にアビジンラベルした Alkaline phosphatase を加えて、PNPP を加えて発色させ測定する。DPPIV 酵素活性は 5F8 抗体で捕捉した可溶性 CD26 プレートに Gly-Pro-pNA を基質として加え測定する。正常人血清中にヒト化 CD26 抗体(YS110)を 1ng/ml、10ng/ml、100ng/ml、1000ng/ml、10000ng/ml、100000ng/ml となるように希釈して加えて上記プレートにて可溶性 CD26 及び DPPIV 酵素活性を測定した。図 1 に示したように正常人 2 症例ともにヒト化 CD26 抗体が 1μg/ml 以上では 1F7 と同一エピトープであるため競合して可溶性 CD26 は検出不能となった。DPPIV 酵素については 5F8 抗体はヒト化 CD26 抗体とは異なるエピトープであるためヒト化抗体存在下でも可溶性 CD26 はプレート上に捕捉され、測定可能であった。

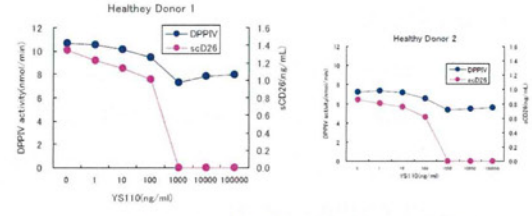

図1 YS110添加時における正常血清中のDPPIV活性およびsCD26 ELISAの影響(1F7-Biotin 標識)

YS110が1μg/m以上では1F7との競合反応により検出不能になる。

2) 市販の可溶性 CD26 ELISA キットにおけるヒト化 CD26 抗体存在下での正常人血清中の可溶性 CD26 の測定

R and D 社及び Bender 社からの可溶性 CD26 ELISA キットを用いて同様に測定した。R&D 社は抗体の一つをポリクローナル抗体、ベンダー社は伴に単クローン抗体を用いた ELISA 系である。図 2 に示すようにヒト化 CD26 抗体添加正常人血清において我々の従来の ELISA 系同様に両者伴に 1μg/ml の点で結合が阻害され、それ以上で測定不能であった。

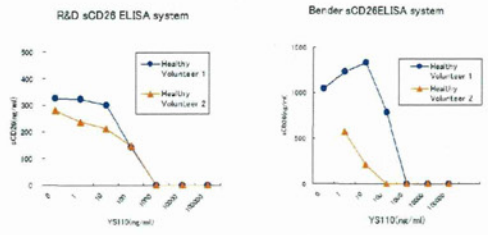

図2 市販ELISAにおけるYS110存在下正常人血清中のsCD26の測定結果

市販ELISAキットも結合阻害により測定不能となる。

3) 独立したエピトープを認識する CD26 抗体の 9C11mAb について

我々は以前に 50 種以上の CD26 単クローン抗体を開発し、13 種の CD26 抗体について 5 つのエピトープ群に分けられることを報告しているが（Mol Immunol 1998; 35: 13-21） 9C11 は 1F7、ヒト化 CD26 抗体と異なるエピトープで、さらに 5F8 が認識するエピトープとも異なる。図 3 に示すように CD26 陽性 Jurkat T 細胞株を用いたが FACS での染色では染色はブロックされることなく全く影響を与えなかった。

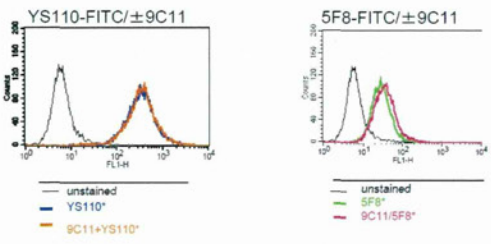

図3 独立したエピトープを認識するCD26抗体9C11mAbの特徴

4) 9C11 抗体を 2 次抗体とした可溶性 CD26 の測定について

9C11 は今まで用いた CD26 抗体とは異なるエピトープを認識することが明らかとなったので、従来の可溶性 CD26 測定 ELISA キットにおいて 1F7 biotin を 9C11 biotin に置き換えて ELISA アッセイを施行した。

図 4 に示すように 9C11 を用いた場合はヒト化 CD26 抗体の存在で sCD26 値はやや低下するものの、1F7 biotin の場合と異なり YS110 が 1μg /ml 以上においても競合せずに測定可能であることが明らかとなった。

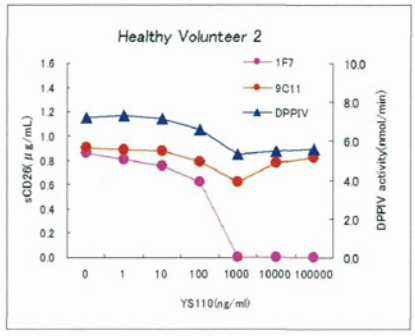

図4 9C11mAbを2次抗体としたsCD26 ELISA測定法は YS110存在下血清でもsCD26を測定可能とした

5) 二次抗体として 1F7 及び 9C11 抗体を用いた種々の検体の測定値比較

従来の 1F7 を用いた ELISA 及び 9C11 を用いた ELISA 法での種々の検体の測定値比較を行った。可溶性 CD26 測定の標準となる組み替え可溶性 CD26 の精製標準品について両者で測定したところ図 5 に示すように R=0.977 及び R=0.982 と両者は非常によく相関した。更に実際の患者の臨床検体（血清、胸水）についても両者の比較をしたところ少数患者で少しのずれが生じているがほぼ両者は相関することが明らかとなった。

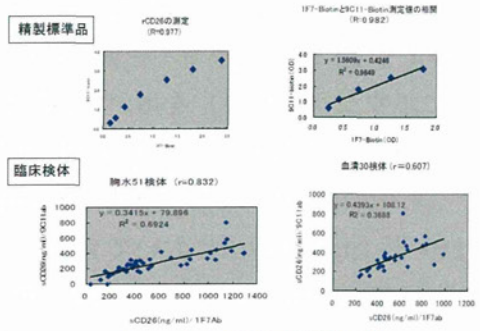

図5 1F7と9C11抗体の測定値比較

D. 考察

今回ヒト化 CD26 抗体存在下でも血清中の可溶性CD26及びDPPIV酵素活性検出可能なサンドイッチ ELISA 法を確立した。悪性中皮腫はアスベストばく露により引き起こされ、30 年～40 年の潜伏期間を経て発生するといわれ、日本では 1990 年前半にアスベスト使用が禁止されたが今後益々増加すると予想されている。東日本大震災での大量のがれき中にもアスベストが含まれており、大きな社会問題となっている。平均生存期間は約 1 年と予後は極めて不良で、新規かつ有効な治療法開発が急務となっている。

悪性中皮腫への新規治療法候補としてヒト化 CD26 抗体を開発し、現在フランスで悪性中皮腫その他 CD26 陽性腫瘍をターゲットとして第 1 相臨床試験を施行中で現在第 5 コホート（4mg/kg）に入っている。第 4 コホートまでの中間評価では安全に進行し、期待される効果も得られつつあり、本邦でもフランスの第 1 相試験が終了次第、臨床試験を計画中である。

現在、糖尿病治療薬として DPPIV 酵素阻害薬が登場し、幅広く用いられつつある。CD26 分子はヒト T 細胞及び腫瘍組織上のみならず可溶性 CD26(sCD26)として血清、胸水中に存在し、DPPIV 酵素活性を含み、GLP-1 をはじめとしてその他サイトカイン、ケモカイン、Neuropeptide 等が基質とされており、これらが切断されることで血糖値を含めて生体の様々な生理学的機能を調節している。

ヒト化 CD26 抗体投与により、血清中に存在する sCD26 と反応し、投与患者では sCD26 値及び DPPIV 酵素値が減少することが予想されることから sCD26 及び DPPIV 酵素活性値を治療経過でモニターにしていくことは抗体療法が安全に施行されるためにも必須である。

今までに可溶性 CD26 測定系として異なるエピトープと反応する CD26 抗体、5F8 及び1F7 を用いたサンドイッチ ELISA 法及び DPPIV 酵素測定 ELISA 法としては固相化した 5F8 に可溶性 CD26 を捕捉させ、Gly-Pro-pNA を加えて、DPPIV 活性を測定する方法を確立した。しかしヒト化 CD26 抗体と 1F7 は同一エピトープを認識する CD26 抗体であるため（5F8 は異なるエピトープ）ヒト化 CD26 抗体治療患者では血清中にヒト化抗体が存在するため従来の CD26 検出 ELISA 系では同一エピトープ sCD26 の 1F7 と競合するために sCD26 は測定できない可能性があったが、予想通りに血清中に 1μg/ml 以上存在する点で測定不能であった。

更に市販の可溶性 CD26 測定 ELISA キットにおいても我々の開発した ELISA アッセイ法同様にヒト化 CD26 抗体 1μg/ml 以上の存在で測定不能であった。すでに開発した CD26 抗体の中で、1F7、ヒト化 CD26 抗体及び 5F8 と異なるエピトープと反応する CD26 単クローン抗体をスクリーニングし

た結果9C11抗体が今までのCD26抗体とは異なるエピトープと反応する抗体であることを同定した。

更に可溶性CD26検出EIISA系においても1F7 biotinの代わりに9C11 biotinに置き換えて、正常人血清にヒト化 CD26 抗体を加えてアッセイを行ったところ競合することなく可溶性 CD26 の測定が可能であった。

精製可溶性 CD26 を 1F7 biotin、 9C11 biotin を用いて測定した結果両者は同等の感度で測定できることが明らかとなった。また実際の患者血清及び胸水においてもsCD26値をほぼ同等に測定していた。

今後は9C11を用いた新しいELISA系でフランスの第 1 相臨床試験検体を測定予定である。血清中のヒト化 CD26 抗体値の動態を解析すると同様にsCD26測定値の変動を検討することは重要であり、また sCD26値、DPPIV酵素活性値とヒト化CD26抗体治療患者の臨床病態や治療効果などを検討することも今後重要と思われる。

E. 結論

ヒト化 CD26 抗体療法下では、患者血清中にヒト化 CD26 抗体が存在し、血清中の可溶性 CD26 と反応して可溶性 CD26 やDPPIV酵素活性が低下することが予想される。従来の我々の開発した 2 つの異なったCD26抗体を用いたサンドイッチELISA法や市販の2種のsCD26測定ELISAキットともにヒト化抗体存在下では測定不能であることが明らかとなった。しかし1F7、5F8、ヒト化 CD26 抗体と反応するエピトープとは異なるCD26抗体9C11を同定し、これを用いることにより、ヒト化 CD26 抗体存在下でも可溶性 CD26 測定が可能なことが明らかになった。

F. 次年度以降の計画

フランスでのヒト化 CD26 抗体を用いた第1相臨床試験患者血清の可溶性CD26値、DPPIV酵素値を新しいELISA系で同定し、患者病態、ヒト化 CD26 抗体濃度などの動きについても検討していく予定である。

G. 研究発表

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H. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

Ⅲ.　研究成果の刊行に関する一覧表

＜研究成果の刊行に関する一覧表＞

【書　籍】

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
青江啓介	悪性胸膜中皮腫と鑑別困難な症例（滑膜肉腫の症例）	独立行政法人労働者健康福祉機構編	アスベスト関連疾患日常診療ガイド（増補改訂2版）	労働調査会	東京	2012	41-42

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IV.　研究成果の別刷

増補改訂2版

アスベスト関連疾患日常診療ガイド

アスベスト関連疾患を見逃さないために

独立行政法人 労働者健康福祉機構 編

日本医師会推薦

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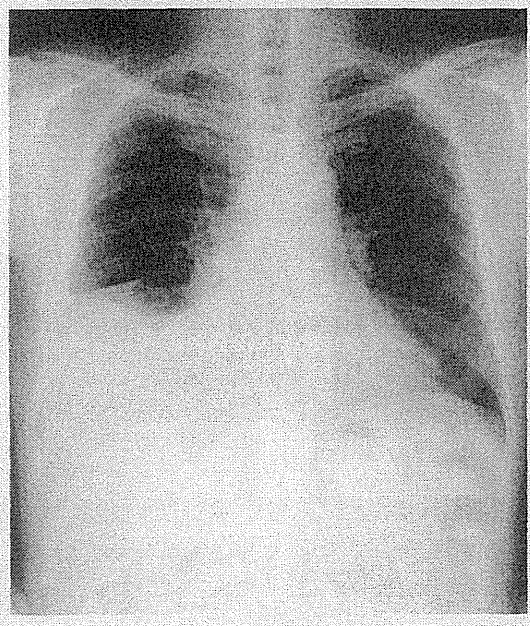
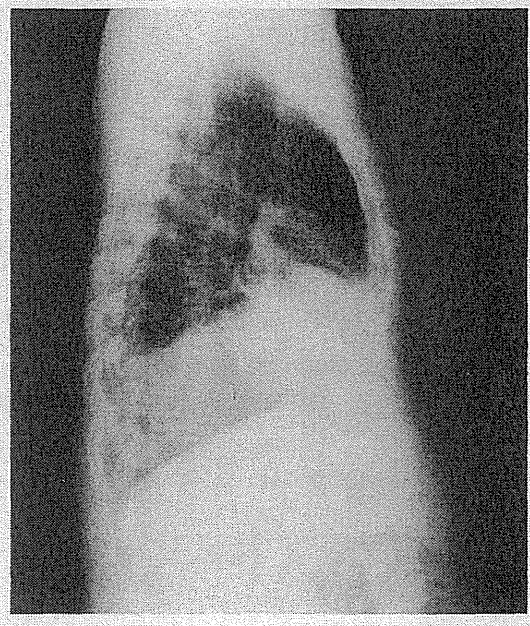
教材用CD-ROM付

写真23　症例1　初診時の胸部X線像





⑧ 症例1―悪性胸膜中皮腫と鑑別困難な症例（滑膜肉腫の症例）

●症例：男性、60歳代

●主訴：右背部痛

●職業歴：元事務系会社員でアスベストばく露歴はなし

●喫煙歴：20本/日（約45年）

●現病歴：1ヵ月持続する右背部痛を主訴に近医を受診した。そして、胸部CTにて右胸水、右胸腔内～右胸壁に腫瘤が指摘された。

●胸部X線（**写真23**）：右胸水貯留が認められる。

●胸部CT（**写真24**、42ページ）：右胸水、右胸腔内～右胸壁に腫瘤が認められる。

●胸部MRI：右胸壁に充実性部分と嚢胞性部分を有する境界明瞭な腫瘤が認められ、腫瘤の大半は胸腔内に存在していることわかる。

●PET-CT：同腫瘤に一致してFDGの高集積が認められるが、腫瘤以外に明らかなFDG高集積は認められない。

●臨床検査所見：胸水検査：TP 5.6 g/dℓ、Alb 3.5 g/dℓ、LDH：218 IU/ℓ、Glu：127 mg/dℓ

●臨床経過：診断及び治療目的に胸壁合併腫瘍切除を行われた。

●病理組織：類円形～楕円形の核を有する小型の腫瘍細胞が束状を呈して錯綜・増生し、腫瘍細胞はほぼ均一で多形性は見られないが、細胞分裂像が多いところで3個/HPF認められ、低分化の悪性腫瘍が示唆された（**写真25**、42ページ）。腫瘍の境界は比較的明瞭で、肋骨への浸潤は認められないが横隔膜への浸潤が認められた（**写真26**、42ページ）。

●免疫組織染色：カルレチニン一部陽性、MNF116（サイトケラチン）陽性、AE1/AE3（サイトケラチン）陽性、Bcl-2 一部陽性、α-SMA（smooth muscle actin）一部陽性、HHF-35（actin）弱陽性、CD99（MIC2）一部陽性、CD34、CD117（C-kit protein）、S-100蛋白、デスミンはいずれも陰性であった。MIB-1 indexは免疫染色の強染が認められた。

以上の結果を総合的に判断し悪性胸膜中皮腫と診断された。シスプラチン＋ペメトレキセドによる全身化学療法などが行われた。腫瘍は化学療法抵抗性で次第に胸膜播種病変が広がり、術後2年の経過で死亡された（**写真27**、42ページ）。

本例は滑膜肉腫に特徴的なSYT-SSX融合遺伝子から生じる融合タンパク質が検出されたため、最終的に滑膜肉腫と診断された。胸膜あるいは胸壁由来の肉腫成分を伴う悪性腫瘍においては滑膜肉腫を念頭に融合タンパク質の検出などを考慮する必要がある。　（青江啓介）

写真24　症例1　初診時の胸部CT像

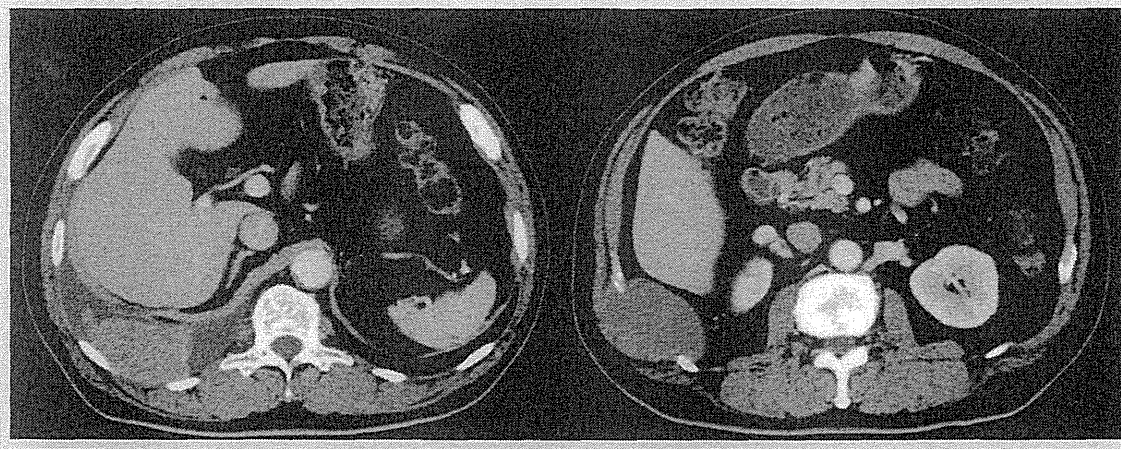


写真25　症例1の組織所見
浮腫状でstoriform patternを呈する部分。

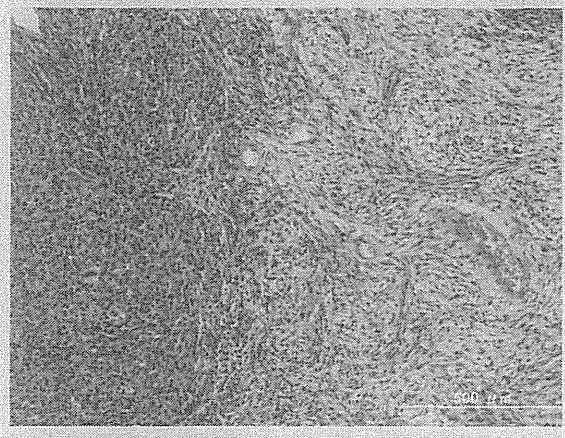


写真26　症例1の摘出標本写真
乳白色充実性で多結節状。所々で出血調。壊死はないが、変性あり。

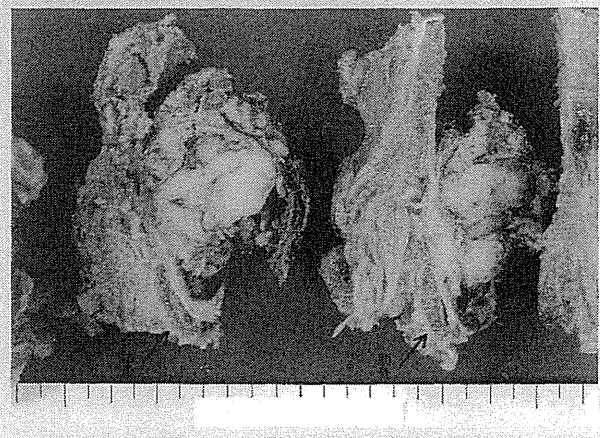
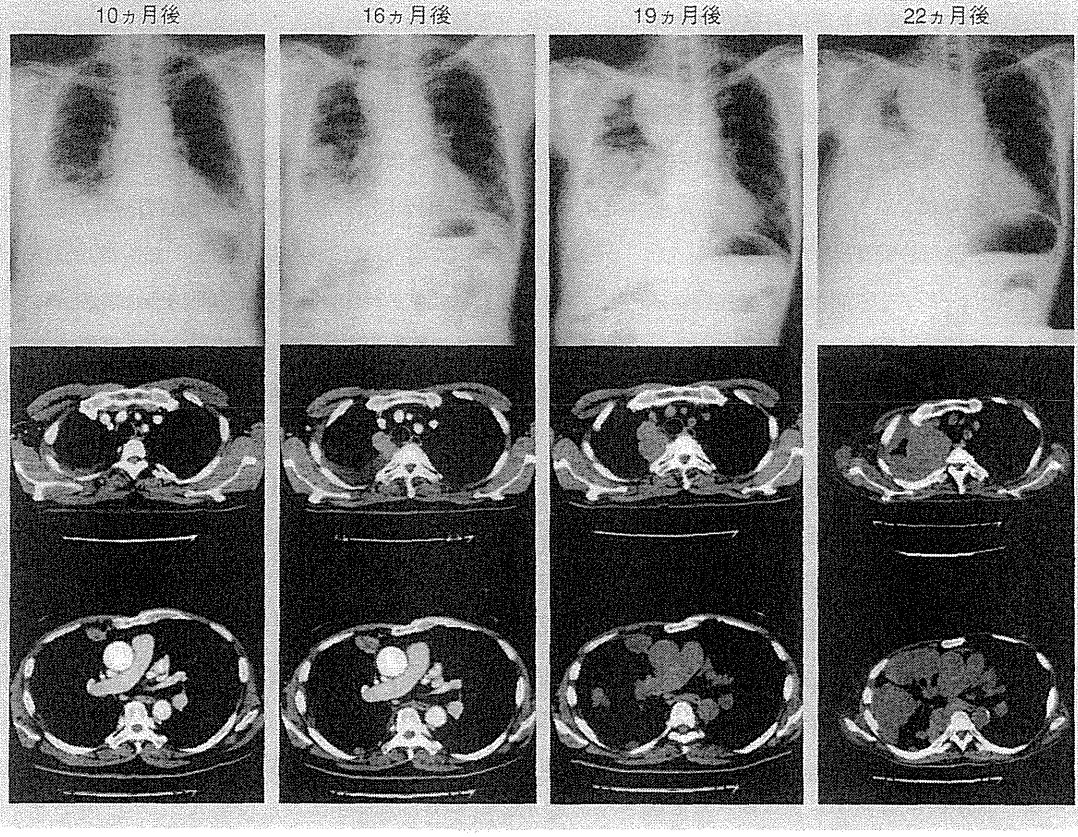
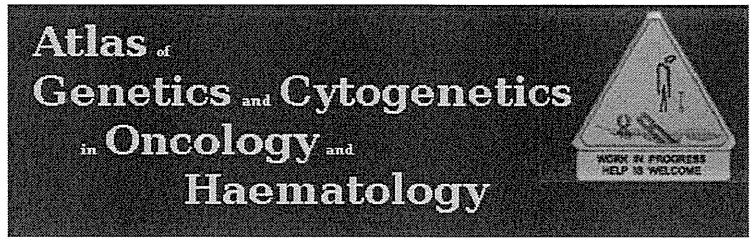


写真27　症例1の術後2年間の経過





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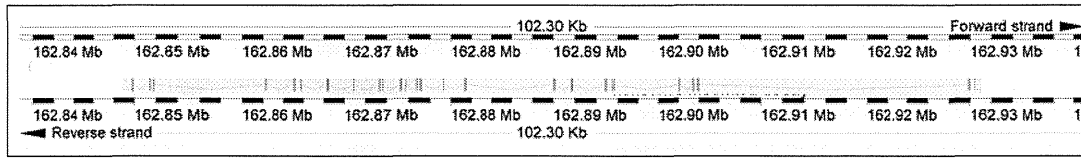
DPP4 (dipeptidyl-peptidase 4)

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]

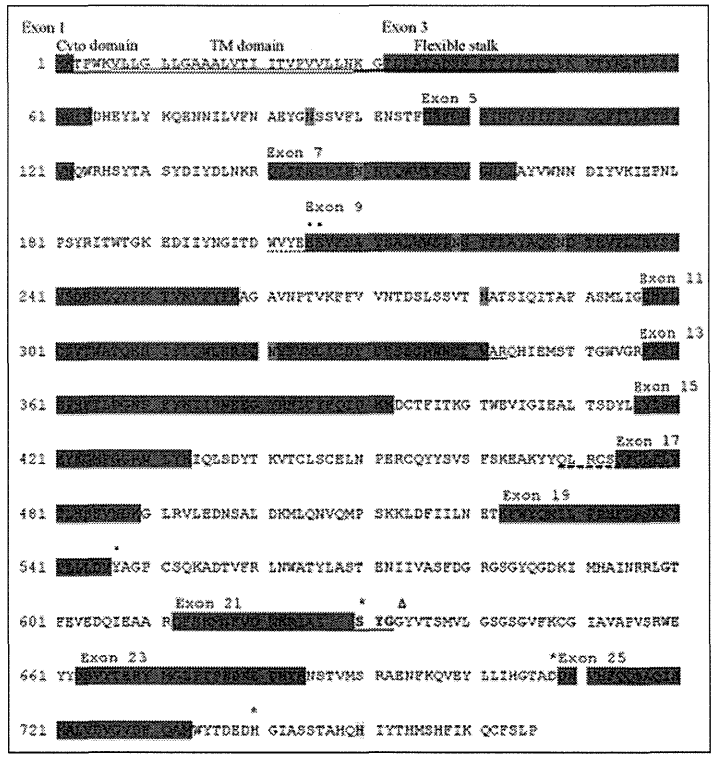


Location of DPP4 gene on chromosome 2q24.3. DPP4 spans 82,301 kbp of chromosome 2 from 162848751 to 162931052. The gene contains 26 exons (indicated in orange squares), ranging from 45 to 1,4 kb in length on the reverse strand. The Ser recognition site (G-W-S-Y-G) is split between exons 21 and 22.

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).

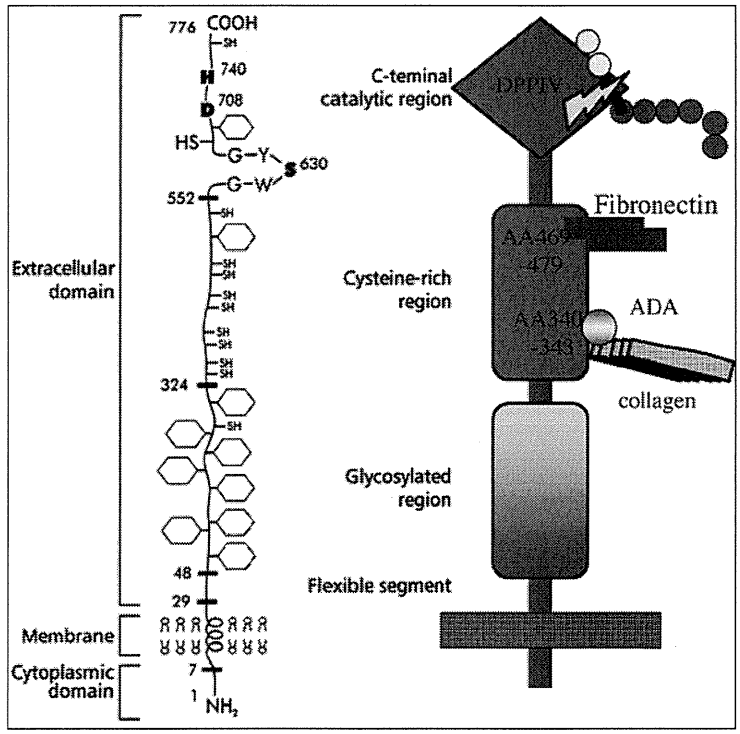
Transcription

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

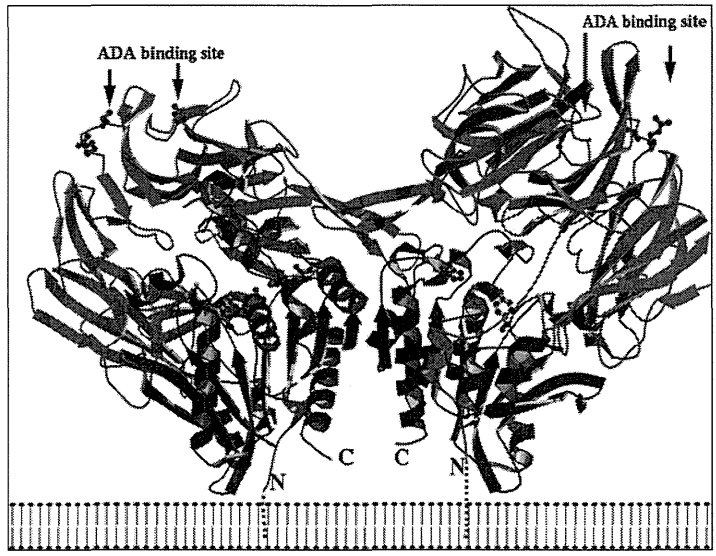
CD26 is a multifunctional type II transmembrane serine peptidase that has an extracellular domain with DPPIV enzymatic activity and a short cytoplasmic domain. It interacts with extracellular molecules and is also involved in intracellular signal transduction cascades. CD26 is important in immunology, 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 **WVY**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.