1 Introduction

CD26, also known as dipeptidyl peptidase IV (EC 3.4.14.5), is a ubiquitous, multi-functional, highly glycosylated type II transmembrane protein (Reutter et al., 1995). It is first described as a glycyl-prolyl-naphtyl-amidase in rat liver homogenates by Hopsu-Havu in 1966 (Hopsu-Havu and Glenner, 1966). Up to now, it has been investigated in the fields of biochemistry, immunology, endocrinology, oncology, physiology and pathophysiology.

1.1 Distribution and expression of CD26/DPPIV

CD26/DPPIV is widely distributed in mammalian tissues, mainly on epithelial and endothelial cell surfaces, on fibroblasts and lymphocytes as well (Reutter et al., 1995). Like other ectopeptidases involved in immunologically relevant functions, such as CD10 (neutral endopeptidase, EC 3.4.24.11) and CD13 (aminopeptidase N, EC 3.4.11.2), the expression of CD26 is strictly ontogenetically controlled during T cell maturation. Among human and murine thymocytes, CD26 is differentially expressed and appears to become up-regulated as thymocytes mature (Ruiz et al., 1996; Ruiz et al., 1998a; Ruiz et al., 1998b). The expression of CD26 on haematopoietic cells is well regulated according to activation status. In human it is expressed on a fraction of resting lymphocytes at low density but is strongly up-regulated following T-cell activation (Fleischer, 1987). In resting peripheral blood mononuclear cells, a small subpopulation of T cells expresses CD26 at high density on the surface ($CD26^{bright}$ cells), which belongs to the $CD45RO^{+}$ population of T cells (memory cells) (Vanham et al., 1993). The number of $CD26^{bright}$ cells and/or CD26 antigen density is higher during the active phase of autoimmune diseases, such as rheumatoid arthritis (Gerli et al., 1996), multiple sclerosis, Graves' disease, Hashimoto's thyroiditis and sarcoidosis (De Meester et al., 1999), and decreased during immunosuppression, as in AIDS (Blazquez et al., 1992; Vanham et al., 1993), Down's syndrome (Bertotto et al., 1994) and common variable hypogammaglobulinemia (De Meester et al., 1999). Moreover CD26 expression on T cells may correlate with T-help subsets. High expression is found on Th1 and Th0 cells, whereas Th2 cells display lower expression (Willheim et al., 1997).

In addition to the integral membrane form, a soluble counterpart of CD26, lacking the intracellular tail and transmembrane regions, is determined by enzyme activity, immunoreactivity and ADA binding (Duke-Cohan et al., 1995; Durinx et al., 2000). Soluble CD26 is considered to be derived from membrane bound CD26 by proteolytic cleavage and is responsible for inactivation of some bioactive peptides. It is found at high concentration in seminal plasma (Wilson et al., 1998), whereas moderate and low amounts are detected in plasma and cerebrospinal fluid, respectively (Iwaki-Egawa et al., 1998). In some diseases its concentration in serum is altered (Hanski et al., 1986; van West et al., 2000).

1.2 Structure of CD26/DPPIV

Alignment of the amino acid sequences of CD26 is highly conserved among different species, with similarities of about 85% between rat and human and 92% between rat and mouse. The C-terminal segment shows the highest level of identity (Ogata et al., 1989; Marguet et al., 1992; Misumi et al., 1992). At the cell surface, CD26 is expressed as a non-covalently linked homodimer comprising two identical subunits of approximate 110 kDa molecular mass. The primary structure of rat CD26/DPPIV consists of 767 amino acid residues. The *N*-terminus of CD26, containing a short cytoplasmic domain of 6 and a hydrophobic transmembrane domain of 22 amino acid residues, serves as both signal peptide and membrane anchor (Hong and Doyle, 1990). The large extracellular domain of CD26 (739 amino acids) can be divided into three regions with specific characteristics. Adjacent to the membrane domain is the *N*-glycan-rich region containing 5 out of 8 *N*-glycosylation sites. These *N*-glycans are essential for folding and biological stability of this molecule (Fan et al., 1997; Fan et al., 2001). In the central cysteine-rich region containing 10 of the 12 cysteines, disulfide bridges are formed providing the formation of a functional conformation of CD26 (Dobers et al., 2000). The C-terminus harbors the active site of this enzyme, which consists of a triad of amino acids including Ser^{631}, Asp^{709} and His^{741} (Ogata et al., 1992; David et al., 1993). Its homodimerization is essential for the enzyme activity (Püschel et al., 1982; Walborg et al., 1985).

CD26 is a member of the POP (prolyl oligopeptidase) gene family with an α/β hydrolyase domain and a β-propeller domain (Abbott et al., 1999; Gorrell et al., 2000; Polgar, 2002). To understand the mechanisms underlying its biological functions, it is necessary to study three dimensional structure of CD26.

1.3 Enzymatic activity and substrates

CD26, a non-classical serine protease, is well known to have dipeptidyl peptidase IV activity in its extracellular domain. It has a high selectivity for peptides with a proline or alanine at the second position and cleaves off dipeptides at the N-terminus of such peptides (Yaron and Naider, 1993). Substrates with Pro are far better hydrolyzed than the corresponding ones with Ala; besides, certain peptides with other small amino acids in second position are also cleaved at low rates (Martin et al., 1993). Since that proline involved in peptide bonds normally contributes to conformation of peptide chains and restriction of hydrolyses by most proteases, the action of CD26/DPPIV is a rate-limiting step and seen as an important 'check-point' in the degradation of polypeptides. An obvious function of this molecule as an enzyme is the degradation of peptides and proteins to small peptides and amino acids suitable for transport and reutilization. It has been shown that CD26 gene deficient rats suffer from severe disturbance in the renal absorption of proline-containing peptides (Brandsch et al., 1995). Another function is to inactivate or activate biological important peptides. Many biologically active polypeptides have the sequence X-Pro at the N-terminus and are potential substrates of CD26. CD26/DPPIV may be essential for modulation their functions. These peptides (Tab. 1, modified from Mentlein (Mentlein, 1999)) include neuropeptides Y, YY, immunopeptides TNF-α (tumour necrosis factor-α), RANTES (regulated on activation normal T cell expressed and secreted) and SDF-1 (Stromal derived factor-1), GLP-1, GLP-2 (peptide homones glucagon-like peptides 1, 2) and GIP (glucose-dependent insulinotropic polypeptide). The cleavage by CD26 results in distinguishable effect on different substrates. For example, truncation of IP-10 (interferon-γ inducible protein) does not abolish its biological activity (Oravecz et al., 1997). While the des (Try-Pro) derivatives of neuropeptide Y and Peptide YY lose their activity at Y1

receptor, but their activities are not or scarcely reduced at the Y2 and Y5 receptors (Gerald et al., 1996). CD26/DPPIV inactivates eotaxin at its main receptor CCR3 and N-terminal truncated product is an antagonist to the intact eotaxin (Oravecz et al., 1997). If we consider a combined effect of CD26/DPPIV and other peptidases, such as CD13 (aminopeptidase N), the number of substrates for CD26/DPPIV is even larger.

However, it also should be considered that not all peptides or proteins carrying proline or alanine in their penultimate position can be cleaved by CD26, such as intact IL-2 and G-CSF (Hoffmann et al., 1993). The peptide becomes less susceptible to cleavage by CD26/DPPIV with increasing length. Peptides up to 80 residues appear to be good substrates. Sequestration of larger proteins may depend on their tertiary structures. Thus although a proline residue is also present at the penultimate position in many cytokines, the size constraints make it less likely that CD26/DPPIV acts directly on these substrates under physiological conditions, which is well demonstrated by Hoffmann and Nausch. Oligopeptides with sequences analogous to the N-terminal part of human IL-1β, IL-2, tumor necrosis factor β and IL-6 are hydrolyzed by purified CD26/DPPIV and aminopeptidase N (Hoffmann et al., 1993). The rate of DPPIV -catalyzed hydrolysis of these peptides is negatively correlated with their chain length (Nausch et al., 1990). In contrast, no degradation is found under their conditions for the intact recombinant cytokines, IL-1α, IL-1β, IL-2, G-CSF and for natural IL-2 (Hoffmann et al., 1993).

Table 1 Mammalian regulatory peptides as substrates for DPPIV

Modified from Mentlein (Mentlein, 1999)

Peptide	N-terminus	Residues no.	Cleavage	Significance
Xaa-Pro peptides				
Tyr-melanostatin	YP-LG-NH2	4	++	Inactivation
Endomorphin-2	YP-FF-NH2	4	++	Inactivation
Enterostatin	VP-DP-R	5	++	Inactivation
β-Casomorphin	YP-F...	7	+++	Inactivation
Trypsinogen pro-peptid	FP-T...	8	+	Questionable
Bradykinin	RP-P...	9	Not	-
Substance P	RP-KP-Q...	11	++	Questionable
Corticotropin-like intermediate lobe peptide	RP-V...	22	+	Probably none
Gastrin-releasing peptide	VP-LP-A...	27	+	Probably none
Neuropeptide Y	YP-S...	36	+++	Inactivation at Y1-receptor
Peptide YY	YP-I...	36	+++	Inactivation at Y1-receptor
Aprotinin	RP-D...	58	+	Probably none
RANTES	SP-Y...	68	+	Inactivation at CCR1, CCR3, but not at CCR5
GCP-2	GP-V...	73	+	Probably none
SDF-1α	KP-V...	68	+	Inactivation at CXCR4
SDF-1β	KP-V...	72	+	Inactivation at CXCR4
MDC	GP-YG-A...	69	+	Inactivation at CCR4
MCP-1	QP-DA-...	76	Not	-
MCP-2	QP-DS...	76	+	Inactivation
MCP-3	QP-VG...	73	Not	-
Eotaxin	GP-A...	74	+	Inactivation at CCR3
IP-10	VP-L...	77	+	Unknown
CXCL11	FP-M...	73	+	Reduction at CXCR3
CXCL9	TP-V...	125	Low	-
LD78β	AP-L...	70	+	Enhancement at CCR5
CCL3-L1			+	Enhancement at CCR1, CCR5
Insulin-like growth factor-I	GP-E...	70	Not	-
Pro-colipase	VP-DP-R...(pig)	101	+	Questionable
Interleukin-2	AP-T...	133	Not	-
Interleukin-1β	AP-V...	153	Not	-
α_1-Microglobulin	GP-VP-T...	168	Not	-
Prolactin	TP-V...(sheep)	198	+	Probably none
Trypsinogen	FP-T...(pig)	231	+	Probably none
Chorionic gonadotropin	AP-D...(a-chain)	243	+	Probably none
Xaa-Ala peptides				
PHM	HA-E...	27	++	Inactivation
GRH-(1-29)	YA-D...	29	++	Inactivation
GRH-(1-44)	YA-D...	44	++	Inactivation
GLP-1	HA-E...	30	++	Inactivation
GLP-2	HA-E...	34	++	Inactivation
Gastric inhibitory peptide	HA-E...	42	++	Inactivation

1.4 The role of CD26 in the immune system

A great number of observations have linked CD26 to the functions of the immune system and, in particular to the functions of T cells. Supporting evidences include: some antibodies of CD26, such as CB.1, AC7, TA5.9 and Tal, can activate T cells; certain antibodies against CD26 and specific inhibitors of its enzymatic activity inhibit mitogen- and antigen- induced T-cell proliferation (Mattern et al., 1993; Reinhold et al., 1993; Tanaka et al., 1993; Reinhold et al., 1997b); CD26 is associated with other important molecules in immune system, e.g. CD45, ADA, and ECM. In addition, exogenous soluble CD26 enhances the tetanus toxoid stimulated proliferation of human T cells (Tanaka et al., 1994; Ohnuma et al., 2001). A model of CD26 dimer action at the T cell surface is shown in Fig. 1.

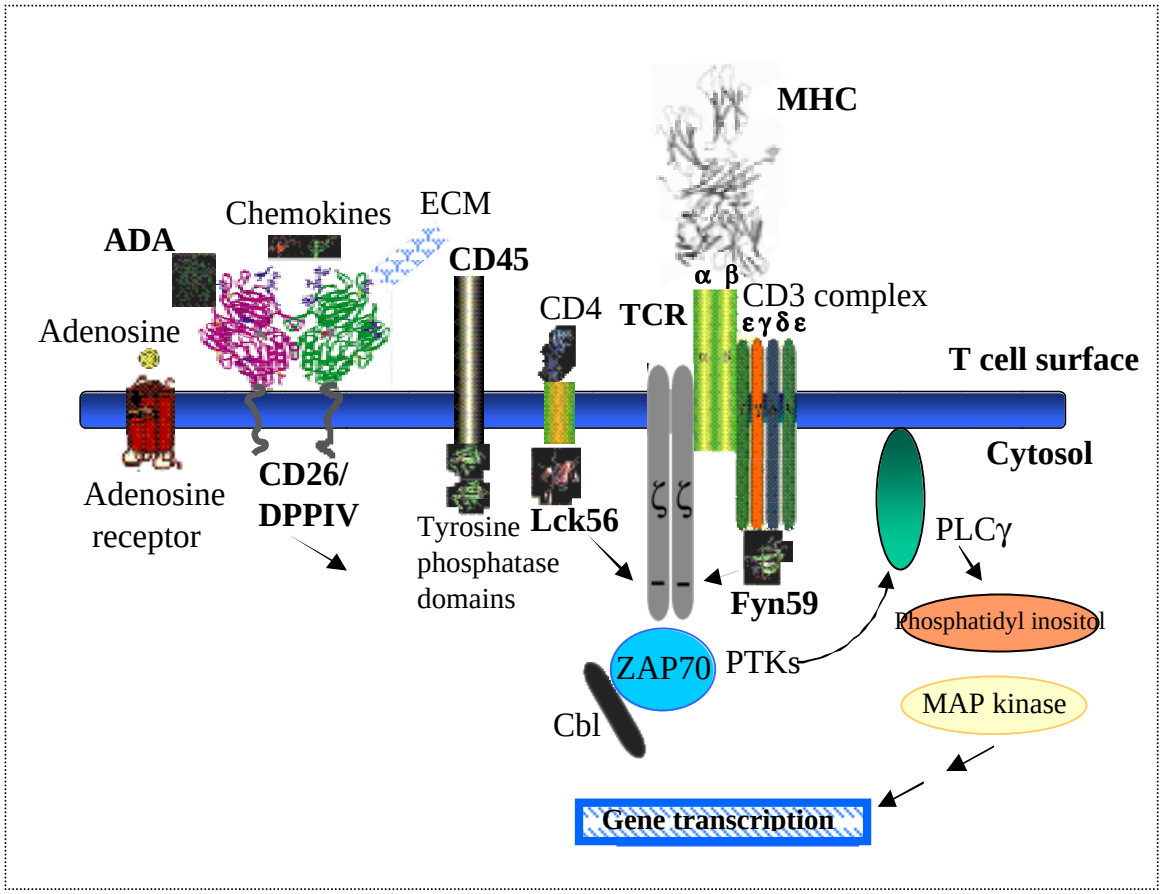

Fig. 1. A model of CD26/DPPIV dimer action at the T-cell surface.

1.4.1 As a co-stimulator in T cell activation

The significance of CD26 in T-cell function is best indicated by the enhancement of CD3 and CD2 dependent activation and proliferation by anti-CD26 antibodies (Fleischer, 1987; Dang et al., 1990a). Only $CD4^+$ cells that coexpress CD26 can provide helper functions to activate cytotoxic T cells (Dang et al., 1990a) and induce immunoglobulin synthesis by B cells (Gruber et al., 1988).

Effective CD26 signaling depends on the surface expression of the TCR/CD3 complex (Fleischer, 1994). This complex plays a central role in T cell activation and function. In general, stimulation through the CD3/TCR complex alone can not induce T cell proliferation and lymphokine secretion. A co-stimulatory signal, which can be provided by accessory molecules expressed on the T cell surface, is required. CD26 is one of such co-stimulator molecules and several distinct anti-CD26 mAbs have costimulatory activities in anti-CD3-driven activation of purified T-cell subsets (De Meester et al., 1995; Hegen et al., 1997; von Bonin et al., 1998). Crosslinking of CD26 by antibody causes tyrosine phosphorylation of an array of intracellular protein involved in TCR/CD3-mediated signal transduction, including ξ chain, p56lck, p59fyn, ZAP-70, mitogen-activated protein kinase (MAPK), c-Cb1 and phospholipase Cγ (Hegen et al., 1997; Kahne et al., 1998).

Whether the DPPIV enzyme activity is involved in T-cell activation is controversial. Upon CD26-mediated costimulation, IL-2 production is higher in Jurkat cells expressing wild type CD26 than in those expressing enzymatically inactive mutants (Morimoto and Schlossman, 1998). However, the enzyme activity of CD26 is reported not to be required for its stimulatory and costimulatory activity by using a mouse TCR^+ T-Cell hybridoma (von Bonin et al., 1998). These results suggest that the CD26/DPPIV enzymatic activity might contribute to, but is not a prerequiste for signal transduction.

Another approach to study the role of enzyme activity of CD26 in immune regulation is the application of specific inhibitors. Inhibiting the enzyme activity of CD26 by specific inhibitors suppresses T-cell proliferation in vitro (Reinhold et al., 1993) and decreases

antibody production in mice immunized with bovine serum albumin (Kubota et al., 1992). The inhibition of the enzyme activity of CD26 abrogates acute rejection, resulting in prolonged allograft survival in a rat cardiac transplantation models (Korom et al., 1999). A significant suppression of IL-2, IL-10, IL-12 and IFN-γ production and an increase of TGF-β (transforming growth factor-beta) are demonstrated in pokeweed mitogen-stimulated T cells by using a series of related competitive inhibitors (Reinhold et al., 1997a; Reinhold et al., 1997b). However, although CD26/DPPIV inhibitors modulated T cell responses, they inhibit cells lack of catalytically active CD26/DPPIV as well (von Bonin et al., 1998). Therefore, the use of inhibitors requires revaluation of the possible unspecific and toxic effects. Except for targeting of CD26 with antibody and /or specific inhibitors, knock out experiments and overexpression of CD26 will provide additional insights into underlying molecular mechanisms.

While, CD26 antigen has a cytoplasmic region consisting of only 6 amino acids, which is too short to fully explain its signal-transducting activity. In this respect, the interaction of CD26 with other signal molecules is demonstrated. Considerable evidences show that CD26 interacts with CD45, a protein tyrosine phosphatase, and adenosine deaminase (ADA, discussed later) (Morimoto and Schlossman, 1998), each of which is capable of functioning in a signal transduction pathway. Recently, it is reported that CD26-mediated signaling for T cell activation occurs in lipid rafts (The detergent-insoluble glycolipid-enriched domains, DIGs) through its direct binding to cytoplasmic domain of CD45. CD26 engagement promotes aggregation of lipid rafts and facilitates colocalization of CD45 to T cell receptor signaling molecules $p56^{LCK}$, ZAP-70 and TCRζ, thereby enhancing protein tyrosine phosphorylation of various signaling molecules (Ishii et al., 2001).

1.4.2 As a binding protein of adenosine deaminase

Adenosine deaminase (ADA) is an enzyme involved in purine metabolism. The function of cell surface ADA is to regulate the concentrations of extracellular adenosine or deoxyadenosine, which are toxic to lymphocytes (Dong et al., 1996). In human, the inheritable deficiency of ADA leads to severe combined immunodeficiency (SCID)

(Magnuson and Perryman, 1986; Blaese et al., 1995; Migchielsen et al., 1995). In 1993, it was demonstrated that CD26 is directly associated with ADA and is identical with ADA binding protein (Kameoka et al., 1993). This binding was found in human, cattle and rabbits, but not in rats and mice (Gorrell et al., 2001). The residues 340-343 on CD26 molecules are essential for this binding. This colocalization only occurs on the cell surface and not inside the cells (Dong et al., 1997). The expression level of cell surface ecto-ADA correlates well with the expression of cell surface CD26, especially in lymphoid cells (Franco et al., 1998). ADA via its interaction with cell surface CD26 can have a co-stimulatory effect in T-cell receptor mediated T-cell activation, which results in an increased proliferation and IL-2 production in Jurkat cells upon stimulation. However, the cell-surface ADA is not directly involved in this process after binding to CD26. In the presence of extracellular adenosine, the transfectants with binding site mutated CD26 are much more sensitive to the inhibitory effect of adenosine and produce less IL-2 than the wild type transfectants. But similar amount IL-2 production between mutated and wild type transfectants is found in the absence of extracellular adenosine. These results suggest that the ecto-ADA bound to CD26 functions in T cell activation by removing extracellular adenosine and thus counteract its inhibitory effect (Dong et al., 1997). Besides, adenosine is known to induce DNA fragmentation in T cells and selectively deplete the $CD4^+CD8^+$ double-positive immature thymocyte subpopulation expressing a higher level $CD3^+$ TCR (Szondy, 1994). The CD26-ADA complex may prevent apoptosis and be involved in thymus differentiation and maturation (Morimoto and Schlossman, 1998).

1.4.3 As a regulator of chemokine function

Chemokines constitute a large group of small (8000–10000 Da) secreted proteins that act as cell-type selective chemoattractants. They can be divided into four subfamilies, based on structural, functional and genetic criteria. Two main subfamilies, CXC chemokines predominantly target neutrophils and, to a lesser extent, lymphocytes, and CC chemokines mainly attract monocytes, but also lymphocytes, basophils, eosinophils, dendritic cells and NK cells. The N-terminal domain of chemokines (together with an exposed loop between the second and third Cys) is involved in receptor binding. Truncation can either activate or

inactivate them, which often occurs only at certain receptor subtypes. In the case of chemokines CD26/DPPIV mediated processing could thus contribute to the regulation of the target cell specificity and consequently to a differential cell recruitment.

Since Oravecz and colleagues first discovered that the receptor specificity of CCL5 is altered by CD26/DPPIV hydrolysis (Oravecz et al., 1997), a number of chemokines have recently been identified as substrates. Despite CD26/DPPIV mediates only a minimal N-terminal truncation, it leads to important alterations in chemokine activities and receptor specificity. Moreover, CD26/DPPIV cleavage can convert several chemokine agonists into antagonists on distinct receptor subtypes. CCL3 (macrophage inflammatory protein-1 isoform LD78), CCL4 (macrophage inflammatory protein-1), CCL5 (RANTES), CCL11 (eotaxin), CCL22 (monocyte derived chemokine), CXCL9 (HuMlG, monokine induced by IFN-γ), CXCL10 (inflammatory protein-10), CXCL11 (IFN-inducible T cell chemoattractant) and CXCL12 (SDF-1α and 1β) are CD26/DPPIV substrates in their natural *in vivo* form (Van Damme et al., 1999). CCL3, CCL5, CCL11, CCL22 and CXCL12, but not CXCL6 or CXCL10, exhibit altered chemotactic activity following CD26/DPPIV-mediated truncation (Van Damme et al., 1999). Notably, the chemokines CXCL2, CCL2 and CCL7 have penultimate prolines but are not hydrolyzed by CD26/DPPIV (Oravecz et al., 1997). These results indicate that CD26 potentially modulates T cell and monocytes extravagation and migration *in vivo*. The receptors for these chemokines are differentially expressed by Th1 and Th2 cells. The cleavage products of these chemokines by CD26/DPPIV trigger Th1 but not Th2-specific chemokine receptor (McCaughan et al., 2000).

1.4.4 Interaction with extracellular matrix protein

CD26 is also described to interact with extracellular matrix proteins, such as fibronectin (Hanski et al., 1985; Piazza et al., 1989) and collagen (Dang et al., 1990b; Löster et al., 1995) by cysteine-rich region, suggesting that it is associated with cell adhesion, differentiation and migration.

1.5 DPPIV-like molecules

CD26/DPPIV is originally believed to be the only membrane-bound enzyme specific for proline as the penultimate residue at the amino-terminus of polypeptide chain. However, recently, a number of DPPIV activity- and/or structure-homologues have been identified and characterized (Sedo and Malik, 2001). Among them, fibroblast activation protein alpha (FAP-α), an integral membrane gelatinase, has 68% homology in primary structure to human CD26/DPPIV and the membrane insertion and the carboxy terminus with the catalytic residues are highly homologous (Scanlan et al., 1994). Other enzymes that cleave dipeptides GlyPro or AlaPro from aminal-terminus of proteins include cell surface molecules: N-acetylated α-linked acidic dipeptidase (NAALADase) (Pangalos et al., 1999), DPPIVβ (Jacotot et al., 1996) and attractin (Durinx et al., 2000), and cytoplasmic protein: DPP8 and quiescent peptidyl peptidase (QPP) (Underwood et al., 1999; Abbott et al., 2000). Several highly homologous proteins of CD26 but without DPPIV enzyme activity have been also discovered, such as DPPX-L, DPPX-S and BSPL (Brain-specific dipeptidyl peptidase-like protein) (de Lecea et al., 1994; Kin et al., 2001). In some cases, CD26/DPPIV and DPPIV-like molecules are co-expressed in one cell, such as CD26/DPPIV, DPP8, QPP and attractin in T cells (McCaughan et al., 2000). Peripheral blood mononuclear cells and kidney from CD26/DPPIV-deficient Fischer 344 rats exhibit 50% and 1%, respectively, of the Ala-Pro hydrolyzing enzyme activity of wild-type (CD26/DPPIV positive) Fischer 344 rats (Smith et al., 1992), indicating that leukocytes do pose not only CD26/DPPIV, but also important DPPIV-like enzyme. Re-expression of CD26/DPPIV rescues expression of FAP-α in melanoma cells (Wesley et al., 1999). Thus their co-action and/or functional substitution should be considered.

Indeed, the most common approach to examine the physiological function of enzyme is to use its specific inhibitor. However, discovery of DPPIV-like enzyme indicates some enzyme inhibitors could have additional effects unrelated to the target protease activity. Most inhibitors previously believed to be DPPIV-specific, were shown to inhibit enzymatic activity of DPPIV-like activity bearing molecules as well. Therefore, reconsideration with caution some former interpretations will be preferred.

1.6 CD26/DPPIV and disease

1.6.1 Type II diabetes

Type II diabetes is a chronic metabolic derangement that results from defects in both insulin action and secretion and leads to overt hyperglycemia. Among substrates of CD26/DPPIV, GLP-1 and GIP are most important incretins known so far. Both hormones stimulate insulin secretion and contribute to physiological glucose homeostasis. Therefore, the use of exogenous GLP-1 and GIP is considered a new therapy to treat type II diabetes. However, their use is limited due to rapid degradation *in vivo* by CD26/DPPIV (Mentlein et al., 1993; Marguet et al., 2000). Two strategies have been developed to improve the pharmacokinetics of GLP-1 and GIP. The first is development of stable peptide analogues that are resistant to degrading enzymes. Some resistant analogues of GLP-1 or GIP have been synthesized and demonstrated to be biologically active to stimulate insulin secretion and subsequently normalise blood glucose. These analogues showed prolonged metabolic stability *in vivo* (Gallwitz et al., 2000; O'Harte et al., 2001; Hinke et al., 2002). Another strategy is to develop inhibitors for enzymatic activity of CD26/DPPIV. A series of CD26/DPPIV inhibitors, diprotin A, Ile-thiazolidide, valine-pyrrolidide, NVP-DPP728 and so on, are demonstrated to be effective to inhibit the truncation of GLP-1 and GIP by CD26 and improve glucose tolerance first by animal models (Deacon et al., 1998; Hughes et al., 1999; Pauly et al., 1999; Pospisilik et al., 2002; Reimer et al., 2002) and later by the preliminary results from human studies (Ahren et al., 2002). Therefore, DPPIV inhibitors and resistant analogues of GLP-1 or GIP are promising new treatments for type II diabetes.

1.6.2 AIDS

Observations, that HIV-infected individuals have significantly lower percentages of cells expressing CD26 at high level in comparison to non-infected controls and that the cells expressing CD26/DPPIV are more sensitive to HIV infection than cells which do not express CD26/DPPIV (Blazquez et al., 1992), boost studies interested in the involvement of CD26/DPPIV in HIV entry. The role of CD26/DPPIV in HIV infection has been controversial. In 1993, Callebaut et al postulated that CD26 is a coreceptor for HIV entry

(Callebaut et al., 1993). But this notion was rapidly contested by others (Broder et al., 1994; Morimoto et al., 1994). The potential roles of CD26/DPPIV in HIV infection relate to altering the HIV-inhibiting capacities of the chemokines CCL5 (RANTES) and CXCL12 (SDF-1α and 1β), binding to gp120 and tat protein of HIV, respectively (Gutheil et al., 1994; Wrenger et al., 1997).

CD26/DPPIV is capable to process RANTES and SDF-1α, with different effects on their anti-HIV activity. RANTES is a chemotactic for lymphocytes, monocytes, dendritic cells, eosinophils, basophils and NK cells expressing CCR1, CCR3 and CCR5. RANTES inhibits HIV infection via its capability of binding to CCR5 (Appay and Rowland-Jones, 2001). Truncation by CD26/DPPIV abolishes the signaling through CCR1 and CCR3, whereas the signaling through CCR5 is retained or even strengthened (Oravecz et al., 1997; Proost et al., 1998), thus results in enhanced anti-HIV activity. By contrast, N-terminal processing by CD26/DPPIV inactivates SDF-1 at its main receptor CXCR4 and significantly reduces the chemotactic and anti-HIV activity of the intact chemokine (Proost et al., 1998; Shioda et al., 1998). Besides, other substrates of CD26/DPPIV involved in HIV infection include MDC (Mantovani et al., 2000), CCL3-L1 (Townson et al., 2002) and eotaxin (Oravecz et al., 1997).

In addition, HIV tat, the transactivation protein, is reported to bind to CD26/DPPIV and reduce the DPPIV activity of CD26, which may decrease costimulatory signaling (Smith et al., 1998; Ohtsuki et al., 2000). Another HIV-related protein, an envelope glycoprotein gp120 inhibits the binding of ADA to CD26/DPPIV and provokes the release of endogenous ADA bound to CD26 by interaction with CD4 or CXCR4 (Valenzuela et al., 1997; Blanco et al., 2000; Herrera et al., 2001).

The overall impact of CD26/DPPIV on HIV infection is still unclear although a lot of evidences support its involvement in HIV entry.

1.6.3 Malignant transformation and apoptosis

Expression of CD26/DPPIV can be extinguished or altered on cancer cells, which has been reported in prostate, colorectal, lung, hepatocellular carcinomas and melanomas and hematological malignancies. CD26 expression during malignant transformation has been characterized in melanocytic cells. Nearly 100% of melanomas lack CD26 expression which is constitutive in normal melanocytes and re-expression of CD26 in human melanoma leads to a loss of tumorigenicity (Wesley et al., 1999). In addition, CD26 expression is shown to be associated with hematological melignancies apoptosis (Aytac et al., 2001; Ohnuma et al., 2002; Sato and Dang, 2003) and inhibits the invasiveness of malignant melanoma cell lines (Pethiyagoda et al., 2000).

1.6.4 Autoimmune diseases/transplantation rejection

The number of lymphocytes expressing CD26/DPPIV and DPPIV enzymatic activity in serum increase rapidly in allograft acute rejection. And the use of inhibitor of CD26/DPPIV resulted in a delay of rejection (Korom et al., 1997). In serum of patients with systematic lupus erythematosus and in synovial fluid of patients with rheumatoid arthritis, CD26/DPPIV activity decreases (Stancikova et al., 1992). The animal models of systemic lupus eryhtematosus also show the same result (Hagihara et al., 1989). However, the clinical signs of experimental autoimmune encephalomyelitis can be suppressed by DPPIV inhibitors *in vivo* both in a preventive and therapeutic fashion. Therefore, DPPIV inhibitors were suggested to be used for immunosuppressive therapy (Reinhold et al., 2002).

Taken together, CD26/DPPIV has been discovered and investigated as a protease and as a binding/co-stimulatory protein. Its crucial role in immunology, nutriology and pathology has been well demonstrated by a huge body of studies. Furthermore, this molecule has become a conspicuous target of drug design. However, it is still a puzzling protein. How it functions awaits further investigation.