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PERSPECTIVES

On the origin of serum CD26 and its altered concentration in cancer patients

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Abstract Dipeptidyl peptidase IV (DPP-IV), assigned to the CD26 cluster, is expressed on epithelial cells and lymphocytes and is a multifunctional or pleiotropic protein. Its peptidase activity causes degradation of many biologically active peptides, e.g. some incretins secreted by the enteroendocrine system. DPP-IV has, therefore, become a novel therapeutic target for inhibitors that extend endogenously produced insulin half-life in diabetics, and several reviews have appeared in recent months concerning the clinical significance of CD26/DPP-IV. Biological fluids contain relatively high levels of soluble CD26 (sCD26). The physiological role of sCD26 and its relation, if any, to CD26 functions, remain poorly understood because whether the process for CD26 secretion and/or shedding from cell membranes is regulated or not is not known. Liver epithelium and lymphocytes are often cited as the most likely source of sCD26. It is important to establish which tissue or organ is the protein source as well as the circumstances that can provoke an abnormal presence/absence or altered levels in many diseases including cancer, so that sCD26 can be validated as a clinical marker or a therapeutic target. For example, we have previously reported low levels of sCD26 in the blood of colorectal cancer patients, which indicated the potential usefulness of the protein as a biomarker for this cancer in early diagnosis, monitoring and prognosis. Through this review, we envisage a role for sCD26 and the alteration of normal peptidase capacity (in clipping enteroendocrine or other peptides) in the complex crosstalk between the lymphoid lineage and, at least, some malignant tumours.

Keywords sCD26 · Dipeptidyl peptidase IV · Cancer · T cells · Chemokines · Incretins

Abbreviations

DPP-IV	Dipeptidyl peptidase IV
ADA	Adenosine deaminase
ADCP	Adenosine deaminase complexing protein

Introduction

The CD26 protein

The exoprotease dipeptidyl peptidase IV (DPP-IV, EC 3.4.14.5), also known as CD26, is a transmembrane glycoprotein of 110 kDa MW expressed constitutively in a dimeric form (220 kDa) on a variety of cell types, particularly prostate, kidney, liver and epithelial cells, predominantly in exocrine glands and absorptive epithelia [1–5], as well as on some endothelial cells of (rat) blood vessels and capillaries [3] and also on lymphocytes [4]. As a special exception, CD26 expression is low in the resting state T and NK cells but it is rapidly up-regulated upon activation of these cells [3–6].

CD26 was originally described in 1966, by Hopsu-Havu and Glenner [7], by its DPP-IV activity in human liver. In 1977, Schrader and Stacy [8] discovered the adenosine deaminase (ADA) binding or complexing protein (ADAbp, ADCP) function. In 1984, Fox et al. [4] described the protein as a leucocyte antigen because of binding of the Ta1 monoclonal antibody. In 1993, the protein was identified as

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CD26 independently by the groups led by Houghton and by Schlossman [9, 10]. It has also been shown to be a functional receptor for collagen and fibronectin, and to interact with the transmembrane tyrosine phosphatase CD45 (in leucocytes), with glypican-3, and with the chemokine receptor CXCR4, as reviewed in [2, 11–14]. A new model for CD26 costimulatory function [13] suggests that, at least in activated memory T cells, CD26 enhances antigen-specific T cell proliferation by engaging signalling pathways in the APCs, in particular the up-regulation of CD86, through the CD26's caveolin-binding domain interaction with caveolin-1, transported to the APC membrane along with the peptide–MHC complex. This interaction also presumably leads to downstream signal transduction in T cell costimulation, in which the cytoplasmic tail of dimeric CD26 may bind to caspase recruitment domain-containing membrane-associated guanylate kinase protein-1 (CARMA).

Therefore, DPP-IV can act in an enzymatic activity-dependent and -independent fashion.

The DASH family

The many proteins, apart from CD26, that exhibit similar DPP-IV activity and/or varying degrees of structural homology are members of the SC clan (representing enzymes with an α/β hydrolase fold) and are known as "DPP-IV activity and/or structure homologues" [2, 15, 16]. These comprise the S9B family, i.e. proteins with DPP-IV activity, from plasmatic membrane (CD26/DPP-IV and FAP-α/seprase) or cytoplasm (DPP8 and DPP9); the S9 family, i.e. DPP6 and DPP10 plasma membrane proteins homologous to CD26 with no peptidase activity (they are involved in neuronal membrane complexes); and the S28 family, a CD26 sequence divergent protein known as DPP7/QPP (quiescent cell proline dipeptidase) or DPP-II, with DPP-IV activity in the lysosomal fraction. There are some excellent reviews on the DASH proteins [15, 16]. Some important facts to consider are (1) there is substantial overlap of substrate specificity and catalytic properties, which indicates the importance of this enzymatic activity, as well as the critical regulation of DASH expression and tissue specificity. (2) The domains unrelated to the catalytic activity are also highly conserved. Together with the fact that the plasma membrane proteins have very short cytoplasmic domains and that they are present in supramacromolecular complexes such as neuronal and lymphocyte synapses or the invadopodia of metastatic cells [17–22], these properties imply evolution of those domains to interact with other functional molecules.

In the context of this review, it is also remarkable that FAP-α, which shares a sequence identity of 50% (and many other similarities such as the size or chromosomal localization) and which may form heterodimers with DPP-IV, has very restricted expression in normal human cells (embryonic and wound healing tissues and pancreatic islet cells), but is selectively expressed on tumour stromal fibroblasts in more than 90% of human epithelial carcinomas such as pancreas, breast, lung and colorectal carcinomas. Some carcinoma cells in melanomas and sarcomas are also positive for FAP-α [21, 23, 24]. In addition to its DPP-IV-like activity, FAP-α has the endopeptidase ability to cleave denatured or unwound type I and III collagens, and therefore may be involved in regulating the extracellular matrix (ECM) of the tumour microenvironment [20–24] (Fig. 1).

CD26 enzymatic activity

DPP-IV activity cleaves two N-terminal amino acids from peptides and small polypeptides with, usually (but not only), proline or alanine in the second position of polypeptidic chains, which are otherwise resistant to most proteases [10–14]. Its first studied role was in the process of dietary protein assimilation on the surface of enterocytes, since DPP-IV enzymatic activity is present in the gastrointestinal tract as a brush border enzyme, and CD26 was used to study the sorting of proteins to the brush border apical membranes, which in this case involved protein glycosylation and lipid microdomains [25–28].

However, many regulatory peptides also contain these sequences [29], and several chemokines, integrins and neuropeptides have been already demonstrated to be cleaved or clipped by this enzyme (clipping has been defined as the proteolytic activation or deactivation of chemokines and other chemoattractants by the removal of short N- or C-terminal peptides; see review [30]) (see Table 1 for known biologically active substrates). Clipping of chemokines by CD26 (some become inactivated and others activated) generally favours the preferential attraction of Th1 cells, and consequently, the recruitment of neutrophils and macrophages (reviewed by Boonacker and Van Noorden [11]).

Although a peptide becomes less susceptible to cleavage by DPP-IV with increasing length (see the excellent review of Lambeir et al. [2]), the fact that several synthetic oligopeptides with sequences analogous to the amino-terminal sequence of several releasing human hormones and cytokines (e.g. chorionic gonadotropin, prolactin, aprotinin, corticotropin-like intermediate lobe peptide and (Tyr-)melanostatin [84], G-CSF, GM-CSF, TNF-β, IL-1β, IL-2, IL-3, IL-5, IL-8, IL-10, IL-11, IL-13, IL-2, thrombopoietin [85], fibrin inhibitory peptide [13, 86]) are hydrolyzed by this protein, also suggests that DPP-IV may participate physiologically not only by itself but also in orchestrated mechanisms with other proteases, particularly aminopeptidase N/CD13 (APN) [87, 88], and matrix metalloproteinases [30, 89].

Most data indicate that glycosylation of CD26 is not a prerequisite for DPP-IV activity, dimerization or ADA

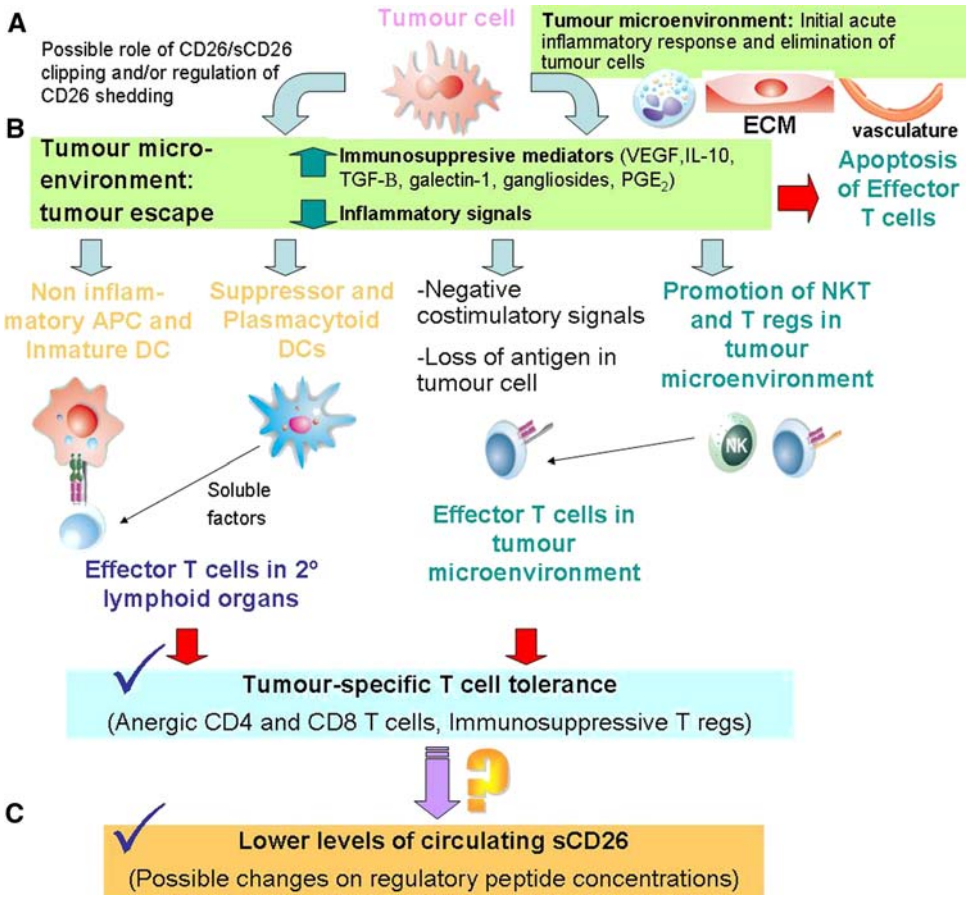

Fig. 1 Scheme of the cancer immunoediting model in which a hypothesis explaining the lower levels of sCD26 found in serum cancer patients is included. **a** The tumour microenvironment (or stroma, composed of epithelial and inflammatory cells, activated fibroblasts, ECM and blood vessels) plays a critical role in tumourigenesis. DPP-IV/CD26 and other DASH proteins play a not wholly known role in the process of tumour progression to malignancy in enzyme activity-dependent and -independent fashions, as reviewed in [2, 11, 14]. **b** According to the cancer immunoediting hypothesis, the escape of tumour variants, which will grow into clinical apparent tumours, develops from cellular and molecular mechanisms leading to immune tolerance. Tumour cells employ a plethora of mechanisms that may act in concert to directly evade effector T cells responses, such as negative costimulatory signals, apoptosis and impairment of the antigen presentation machinery. However, the dominant mechanism which renders T cells tolerant during tumour growth is to change the tumour microenvironment through secretion of many immunosuppressive mediators and absence of some inflammatory mediators. This network leads to: problems in tumour antigen processing by APCs, particularly DCs, and later presentation to T cells in secondary lymphoid organs; the inhibition of DC maturation and differentiation; and the recruitment of different regulatory populations (NKT cells, Tregs, subsets of myeloid and plasmacytoid DCs, and others) [174, 338]. **c** As consequence, effector T cells become anergic after tumour-specific Ag presentation. A huge amount of information supports T cells as a major source of circulating sCD26. Serum concentration of sCD26 is significantly lower in patients of some cancers (see text). Taking into account these facts, we propose that tumour-specific tolerant cells or a subset of regulatory cells may be responsible of sCD26 lower concentrations in cancer patients. This drop in sCD26 may have further consequences

binding [90, 91] but that certain specific glycosylations can profoundly affect the enzyme activity [92].

In conclusion, the enzyme is currently viewed as having a dual function, depending on the tissue: in changing the functional activity of its substrates as well as a checkpoint to general proteolytic degradation [2, 11, 16].

CD26 as a therapeutic target

Many inhibitors of DPP-IV are currently under investigation (some of them reviewed in [2]). Haematopoietic stem cell transplantation [68, 83, 94] and some T cell-dependent inflammatory diseases [87, 88, 94] will soon start clinical trials. In clinical Phase II and III trials, ValboroPro (Talabostat) was originally intended to inhibit FAP, but is a non-selective dipeptidyl peptidase inhibitor that has been tested in patients with lung, pancreas and colon cancer, and with melanoma and chronic lymphocytic leukaemia [21, 23, 24, 95]. Two inhibitors have already been approved for use in the European Union (sitagliptin, MSD and vildagliptin, Novartis), and the first also in the US, for the treatment of type 2 diabetes.

Table 1 Peptides with known physiological activity that are cleaved by dipeptidyl peptidase IV enzymatic activity

Substrate families	Peptides	Biological effect	Species (in vitro/in vivo)	References
Incretins and gastrointestinal hormones	GLP-1	Inactivation Possible cardiovascular role of the product	Human (in vivo) Dog (in vivo)	[31–34] [35]
	GLP-2	Inactivation	Human (in vivo)	[36]
	GIP	Inactivation	Human (in vivo)	[37, 38]
	Glucagon	Inactivation	Human (in vivo)	[39, 40]
	PACAP[a]	*Inactivation*	Human (in vitro)	[41]
	GRP	Not known	Human (in vitro) Product in dogs	[41, 42]
	Peptide YY[a]	Change in receptor preference	Human (in vivo) Rat (in vivo, vasoactive action)	[43–47]
Vasoactive peptides	Bradykinin	Change in receptor preference or inactivation (in conjunction with APN)	Human (in vivo, indirectly) Rat (in vivo)	[48–51]
	VIP	*Inactivation*	Human (in vitro)	[41]
	BNP[a]	Change in receptor preference or Inactivation	Human (in vitro) Product in dogs	[52, 53]
Neuropeptides	NPY[b]	Change in receptor preference	Human (in vivo, indirectly) Rat (in vivo)	[48–51] [54–56]
	Beta-casomorphins	Inactivation	Human (in vivo, indirectly) Rat (in vivo)	[57, 58]
	Endomorphins	Change in receptor preference	Rat (in vivo) Mouse (in vivo)	[51] [59, 60]
	Substance P	Inactivation	Rat (in vivo) Pig (in vivo) Human (in vitro)	[51, 59–63]
Chemokines	CCL3 (MIP-1α, LD78β)	Enhanced activity Change in receptor preference	Human (in vivo, indirectly)	[64, 65]
	CCL4 (MIP-1β)	Change in receptor preference	Human (in vivo, indirectly)	[66, 67]
	CCL5 (RANTES)	Change in receptor preference	Human (in vitro, indirectly)	[68–70]
	CCL11 (Eotaxin)	Inactivation	Human (in vitro) Rat (in vivo)	[71, 72]
	CCL22 (MDC)	Change in receptor preference	Human (in vitro)	[73]
	CXCL6 (GCP-2)	No changes	Human (in vitro)	[68]
	CXCL9 (MIG)	Inactivation	Human (in vitro)	[74, 75]
	CXCL10 (IP-10)	Inactivation, CXCR3 antagonist	Human (in vivo, indirectly)	[74, 76]
	CXCL11 (I-TAC)	Inactivation, CXCR3 antagonist	Human (in vivo, indirectly)	[74, 77, 78]
	CXCL12 (SDF-1alpha)	Inactivation, CXCR4 antagonist	Human (in vivo)	[79–83]

Biological effect in italics refers to hypothesis. Species (in vivo/in vitro) refers to: In vivo, the existence of studies in humans or other species with inhibitors as well as the existence of the product and well-known biological effects of peptides; *indirectly* refers to the lack of in vivo studies with inhibitors. In vitro, studies not fulfilling these parameters

[a] Peptides belong also to the neuropeptide group

[b] Peptides belong also to the vasoactive group

This new class of drugs for the treatment of diabetes acts by enhancing the half-lives of the incretins (GIP and GLP-1), which induce insulin secretion, leading to a sustained reduction in blood glucose levels [96, 97]. The large insulin response to ingestion of a meal is mainly due to the effects of these hormones released into the circulation by K and L cells located in the gastrointestinal tract [96–98]. Both have short half-lives (5 min; active peptides, 2 min) due in part to rapid inactivation by DPP-IV, which limits the effects of GLP-1 and GIP on glucose homeostasis [96]. The inactivation may occur partially on the endothelial cells of the capillary vessels that drain the intestinal mucosa, as has been demonstrated in pigs [33], although only a tenuous DPP-IV

activity and immunostaining have been described directly in human, mouse and rat intestine endothelia [2, 3, 99]; and partially by soluble protein DPP-IV existing in capillary blood [32, 99, 100], before GLP-1 enters the portal circulation [96].

No immediate adverse or secondary effects resulting from the therapeutic alteration of DPP-IV activity in controlled clinical studies have been reported by the manufacturers [except a small increase in nasopharyngitis with sitagliptin, but not with vildagliptin (product monographs for Januvia, MSD and for Galvus, Novartis)], although obviously no long-term studies have been carried out. As preclinical animal studies identified several problems, possibly due to cross-enzymatic inhibition (at least DPP8 and DPP9) [101, 102], and the enormous number of substrates (Table 1), see [48], vigilance over long-term use of inhibitors is mandatory [103, 104].

CD26 in cancer

CD26/DPP-IV has been consistently associated with cancer since it was known as ADCP, or the 2 or Large ADA isoform [105, 106]. It is important to point out that these studies with ADCP involved immunological techniques and are therefore more specific than earlier studies that measured the DPP-IV enzymatic activity in tumour tissues. The group led by Bosman found that ADCP staining was decreased in about one-third of colorectal, prostatic and renal tumours, but unaltered or even increased in the other two-thirds; significant intratumour and intertumour heterogeneity as well as differences in the cellular staining pattern with respect to the normal tissue were also reported [107–110]. It should be also pointed out that the non-enzymatic role of CD26 as an extracellular anchorage for ADA may be important in tumourigenesis. Although the presence of extracellular ADA is independent of PM CD26 expression [111–114], the ADA–CD26 complexes may participate in cell-to-cell contacts [18, 113, 115] or, more probably in this context, through the catalysis of adenosine to inosine [112–114]. Proliferating cells accumulate high extracellular concentrations of adenosine, a purine nucleoside found within the interstitial fluid of solid tumours, which may be toxic or influence the proliferative potential of a cell, depending on the relative expression, and type, of adenosine receptor (AR). Therefore, the different levels of cell surface CD26–ADA complex and relative expression of ARs on a tumour cell may lead to generation of tumour subclones as well as to participation in the well-known adenosine inhibition of cell-mediated immune responses to tumour cells [16, 114, 116–120].

Pro-oncogenic activities

In addition, it has recently been reported that CD26–ADA may form a ternary complex with plasminogen. Binding of plasminogen to cell surface receptors promotes its conversion to plasmin, which is required for proteolysis of the ECM in several physiological and pathological processes, including cell migration, tumour cell invasion and metastasis [120].

Many reviews have discussed the role of CD26/DPP-IV activity in cancer and the potential usefulness of this protein in therapeutics and diagnostics [12, 16, 116, 121]. It is important to note that early studies measured the DPP-IV enzymatic activity in tumour tissues and body fluids, as already mentioned, but some DASH proteins also use strikingly similar substrates. For example, the enhanced DPP-IV and DPP-II activity observed in lung squamous cell carcinoma as compared with that in normal lung tissue [122–124] may be related to the well-established FAP expression in that tumour [125]. In addition, glypican-3 has been recently reported as the first natural inhibitor of CD26/DPP-IV enzymatic activity, in in vitro experiments [126]. Glypican-3 is one of the six mammalian glypicans (heparan sulphate proteoglycans GPI-linked to the cell membrane) that are usually expressed during development and are basically absent from adult tissues but up-regulated in many tumour tissues [127]. Therefore, a possible glypican-3-dependent DPP-IV inhibition may also lead to levels of enzymatic activity in the tumour being independent of the actual amount of CD26. It appears that glypican-3 can modulate the activity of many growth-signalling peptides, such as insulin-like growth factor 2, and that it is related to apoptosis and confers oncogenicity to the cell [16, 128, 129].

FAP-α also appears to be pro-oncogenic and its collagenolytic or gelatinase activity at the invadopodia supramolecular complex, implicated in ECM remodelling during tumour invasion, metastasis or angiogenesis, is well established [15, 16, 20–24, 130]. Therapies targeting FAP inhibit tumour growth [95, 131], and FAP is selectively expressed on stromal fibroblasts of various epithelial carcinomas, such as pancreas, breast, lung, esophagic, gastric and colon cancers, as well as in melanoma, cervical and brain tumours, as commented [15, 16, 20–24, 130, 132, 133]. The possible usefulness of FAP as a marker of (poor) patient prognosis in cervical, colon and ovarian cancer has recently been well reviewed by Sedo et al. [16].

CD26, also present at the invadopodia, together with other ectoproteases and metalloproteases [21, 130, 134], can participate in malignant transformation and cancer progression through its ability to bind collagen and fibronectin [20–22, 116, 121, 130, 135]. MMPs, including MMP-2 and MMP-9, and FAP digestion of ECM components will permit passage of the malignant cells through basement

membranes and stromal barriers. This pro-oncogenic behaviour is thus consistent with the non-enzymatic interactions with cell surface ADA–plasminogen and glypican-3 mentioned above, and the formation of FAP–CD26 heterodimers, although it is not known whether these heterodimers have a different function from homodimers (in fact they are not co-expressed in tumour stromal fibroblasts or sarcomas) [130, 136]. A clue to later discussion is that glypican-3 may inhibit the enzymatic activity of CD26 in this context, i.e. in a particular tumourigenic niche [137].

The up-regulated CD26 expression associated with the aggressiveness of T and B lymphomas and leukaemias [138–141], thyroid follicular, papillary carcinomas, astrocytic tumours and gastrointestinal stromal tumour [142–145] are consistent with these findings. Very recently, CD26 expression was evaluated in various peripheral B-cell lymphoid tumours: CD26 expression was absent or barely detectable in follicular and mantle cell lymphomas, high in multiple myelomas and hairy cell leukaemias, and variable in chronic lymphocytic leukaemias, in CD5(neg) B-cell chronic lymphoproliferative diseases and in diffuse large cell lymphomas. In B-CLL, CD26 expression on cell surface (analysed by flow cytometry [146]) and CD26 gene overexpression (analysed by microarray technology [147]) may identify subsets of patients with an unfavourable clinical outcome, thus suggesting its potential role as a prognostic marker of progressive disease. The enhanced DPP-IV activity (not necessarily CD26 specific) found in early lung squamous cell and skin basal cell (and precancerous dermatosis) carcinomas, prostatic tumours and hepatocellular carcinomas [148–150], which is then lost in later phases (probably due to a transition from early invasive stages), as well as the higher CD26 expression in benign melanoma (compared with a decrease in malignant melanomas) [151], and the demonstrated use of mAb anti-CD26 as treatment for mesothelial and renal cancers [152, 153] may also support these findings.

Anti-oncogenic activities

There is a fundamental difference between CD26 and the other proteases involved in cancer development and progression as executors of ECM degradation: CD26 is constitutively expressed in the tissues mentioned at the beginning of this article, and its enzymatic activity regulates the biological activity of regulatory peptides, growth factors and chemokines. If glypican-3-dependent local DPP-IV inhibition can be confirmed in a physiological context, this indicates a natural protective role for the enzyme that should be blocked in the tumourigenic process.

This idea was proposed early on following the immunohistological studies cited above [107–110], which reported a loss of CD26 expression in some tumour tissues, and from other studies that found significant decreases in DPP-IV activity [16, 117], not only in the tumour microenvironment but also in the systemic circulation (see further below). In addition to some prostatic, colorectal, haematological and renal tumours [107–110, 154–157], a decrease in CD26 was found to accompany the progression of melanoma lesions, and CD26 was absent from metastatic tumours [151, 158]. An inverse correlation between CD26 expression and the grade of tumour was also observed in endometrial cancers [159, 160]. Interestingly, in advanced stages from prostate and lung and skin squamous cell carcinomas [161, 162], CD26 expression is lower than in early stages, or may even be absent.

The protective role was first contrasted in 1999 by the Houghton's group [163–166] when they reexpressed wild-type or mutant CD26 transfected in human melanoma cells at levels comparable to those found in normal melanocytes and observed reversions of the malignant phenotype: an enzymatic activity-dependent loss of tumourigenicity and abrogation of a block in differentiation, as well as enzymatic activity-independent re-emergence of dependence on exogenous growth factors for cell survival. They found similar or additional tumour suppressor functions for CD26 reexpressed in vitro in cell lines from non-small cell lung and prostatic carcinomas [167, 168], and concluded that DPP-IV regulates the activities of (unidentified) locally produced mitogenic peptides involved in cancer development. Similar changes in morphology, as well as decreased growth, migration and adhesion, and changes in E-cadherin and MMPs and TIMPs cell surface expressions were recently described for ovarian carcinoma and glioma cells [169–171].

Together these data—differences in the cellular staining pattern with respect to the normal tissue, significant intratumour heterogeneity and changes of CD26 expression linked to the transition of tumour stages—indicate a quite complex situation in the physiological microenvironment of cancer niches. The possibility that the tumourigenic process may manipulate the functions of CD26/DPP-IV, e.g. evading the immune system by modifying local chemokine gradients (and therefore, the immune cell homing), and by modulating cytokines and angiogenic or immunosuppressive factors (Table 1) [89, 172–176] deserves to be studied in more detail. Nevertheless, some diagnostic and prognostic uses for tumour CD26 expression have been proposed (and reviewed in [2, 16, 119]).

Serum CD26

Significant levels of DPP-IV activity have been shown to occur in body fluids such as plasma, serum, cerebrospinal and synovial fluids, semen and urine (see reviews [2, 11–13, 16]).

Serum DPP-IV activity was discovered in 1968 by Nagatsu's group in Japan [177]. It is very important to note that there is no direct correlation between serum CD26 (or soluble, in contrast to transmembrane) (sCD26) protein concentrations and serum enzymatic activity assays, for three reasons: (1) There are some circulating proteins other than CD26 with DPP-IV activity, as will be discussed below. (2) Sialylation (a type of glycosylation) of sCD26 [2, 11–14, 92] is strongly enhanced in elderly individuals [178], and the recent finding that a certain type of hypersialylation can inhibit DPP-IV activity [93] is consistent with the fact that serum/plasma DPP-IV enzymatic activity tends to decrease with age [2]. The slight but significant decrease of the serum sCD26 protein levels we have observed in a large cohort (data submitted) is not enough to explain the decrease in activity. (3) It has recently been suggested that the serum protein attractin, which has a CUB domain (a motif of around 110 amino acids residues present in multiple plasma membrane-associated proteins) that enhances the enzymatic activity of tolloid proteases [179, 180], may regulate the DPP-IV activity of CD26/sCD26 in the same way [16]. Attractin is the product of the mahogany (human ATRN) gene involved in control of pigmentation, energy metabolism, immune status and neurodegeneration [181]. Once thought to have DPP-IV activity itself [182–184], serum attractin has both secreted (with isoforms) and membrane forms that result from an alternative splicing that it is differentially regulated at least in lymphoid tissues [185], and is actually frequently co-purified with sCD26 [16, 182–184].

The protein

Within normal plasma/serum, some 90–95% of DPP-IV activity has been associated with a relatively high concentration of sCD26 in human serum (~600 μg L^{-1}) (Table 2) [2, 16, 186–188]. Since sCD26 is heavily glycosylated, its molecular weight is similar to that of transmembrane CD26 [186, 188] although it lacks transmembrane and cytoplasmic domains (the sequence starting at the 39th position) [187]. Iwaki-Egawa et al. [187, 189, 190] suggested that sCD26 must be shed from any plasma membrane on CD26 expressing cells that are in contact with blood, by proteolytic cleavage, which is analogous to the findings of some differently processed derivatives of other PM proteases such as APN (lacking 59 or 68 amino acid residues) in normal and maternal or pregnant serum. Other natural or recombinant sCD26 proteins are similar, but not equal, to the naturally occurring soluble form (reviewed by Gorrell et al. [14]).

A diverse range of PM proteins of Type 1 or Type II topology that also occur as a circulating, soluble form are derived from the membrane by a group of enzymes referred to collectively as 'secretases' or 'sheddases' [191]. The facts that only one CD26 mRNA form is usually reported [146, 192, 193], and that it is transported from its site of synthesis in the rough endoplasmic reticulum to the microvillar membrane of enterocytes and some cell lines in a membrane-bound state [11, 14, 27, 28, 194], also suggest that it is not secreted. It is important to point out that the shedding of most integral membrane proteins is regulated, often by a PKC-dependent mechanism [30, 195, 196].

However, CD26 has been found to be soluble in the lumen of secretory granules. In endocrine pancreatic A cells, accompanying glucagon, both undergo exocytosis to the interstitial space where sCD26 may act on secretory products of neighbouring islet cells [197, 198]. In this case, another possible mechanism for the release of CD26 from the membrane is autolysis of the protein (as observed in vitro) [199] by the acidic pH conditions found inside the granules [198]. In addition, as the amount of sCD26 decreases during granule maturation, this suggests that the protein is sorted (a pathway already observed with other secreted proteins such as the insulin C-peptide) [198], which is another example of the particularity of CD26 gene expression, i.e. it is mostly regulated at the posttranslational level. Although some regulation at the transcriptional level has been found in recent times, particularly in B and T cells, in spite of the housekeeping features of the gene promotor [11, 192, 200–202], the first striking result was found in T cells by Mattern et al. [203]: only around half of the T cell population expresses cell surface CD26 despite the fact that both CD26+ and CD26− have similar CD26 mRNA and intracellular protein concentrations, and 4–8 h after T cell stimulation most or all cells express surface CD26 (the intracellular pool is translocated to the cell surface). We also described cytokine-dependent CD26 translocation to the T cell surface related to glycosylation events, and interestingly, observed two different mRNA transcripts by Northern blot in these immune cells [204]. It has recently been shown that rotavirus infection of enterocytes inhibits translation of CD26 but not mRNA transcription [205]. Furthermore, as already mentioned, sCD26 and membrane CD26 present a considerable and tissue-specific molecular heterogeneity originated mainly but not exclusively from different glycosylations [85, 194, 206, 207]. At least in T cells, mitogenic stimulation changed the enzymatic and immunoreactive patterns of molecular CD26 as well as the subcellular localization of the distinct forms [85] and CD26 has been found in endosomes in a process of recycling [208, 209].

Another possibility not yet fully explored and related to the intracellular sorting is the secretion of soluble proteins through MMP-dependent shedding from exosomes. Exosomes are small membrane vesicles derived from intracellular multivesicular bodies (MVBs, formed from the late endosomal compartment) that can undergo constitutive and

Table 2 Studies showing physiological and pathophysiological levels of sCD26 concentration measured by ELISA in human serum (sometimes plasma)

Disease	Concentration ± SD ($\mu g\ L^{-1}$)[a]	Cohort (*n*)	References
Healthy	591 ± 179	38	Bender MedSystems Chemicon/Millipore insert
Healthy	415 ± 96	36	R&D Systems insert
Healthy/	560 ± 126	52	[241] (Bender MedSystems)
Colorectal cancer/	262 ± 138	110	
Gastric cancer	585 ± 148	9	
Healthy/	557 ± 181	2,673	[243] (Bender MedSystems)
Colorectal cancer	312.9 ± 102.4	12	
Healthy/	2,270 ± 770	45	[234] (rabbit Ab)
Oral cancer (SCC)	1,500 ± 350	25	
Healthy/	590 ± 81	11	[246] (Bender MedSystems)
Rheumatoid arthritis	505 ± 142	13 inactive RA	
	403 ± 97	16 active RA	
Healthy/	113	–	[247] (Chemicon/Millipore)
Rheumatoid arthritis	100	22 MTX-nonresp	
	95/73	8/4 MTX-resp	
Healthy/	1,030 (median)	25	[92, 248] (monoclonal Ab BA5)
Rheumatoid arthritis/	850 (median)	25	
Lupus erythematosus/	420 (median)	10	
Sjögren syndrome/	450 (median)	10	
Myocardial infarction	1,900 (median)	10	
Healthy/	–		[7] (Bender MedSystems)
Osteoarthritis	~600 (from figure)	26	
Rheumatoid arthritis	~450 (from figure)	41	
Healthy/	15,600 ± 2,400	54	[249] (monoclonal Ab 1F7 and 5F8)
Systemic lupus erythematosus	7,900 ± 2,400	12 active	
	11,300 ± 3,300	41 inactive	
Healthy/	182 ± 29	26	[250] (Bender MedSystems)
Scleroderma	160 ± 53	30 limited sclerosis	
	126 ± 40	26 diffuse sclerosis	
Healthy/	398 ± 100	35	[251] (Bender MedSystems)
Allergic asthmatics	526 ± 120	51	
Healthy/	540	12	[252] (Bender MedSystems)
Atopic dermatitis	710	88 (do not change with exacerbation nor therapy)	
Healthy/	411	15	[253] (Bender MedSystems)
ANCA-associated vasculitides	258	15 WG (G) active	
	295	15 WG (G) recession	
	316	6 WG (localized)	
	188	16 CSS active	
	257	17 CSS recession	
	283	7 MPA active	
	228	14 MPA recession	
Healthy/	14.9 ± 3.1 $mg\ L^{-1}$	79	[254] (monoclonal Ab 1F7)
HIV-1	15.6 ± 7 $mg\ L^{-1}$	90	
Healthy/	200.6 ± 60.3	20	[255] (Bender MedSystems)

Table 2 continued

Disease	Concentration ± SD ($\mu g\ L^{-1}$)[a]	Cohort (*n*)	References
HCV (chronic)	140.4 ± 63.9	33	
	115.9 ± 32.9	33	
Healthy/	~140 (from figure)	10	[256] (Chemicon/Millipore)
HCV	~185 (from figure)	19	
Healthy/	630	27 (mean 6 years old)	[257] (Bender MedSystems)
Visceral leishmaniasis	890 active	33 (mean 3.6 years old)	
	995 asymptomatic	15 (mean 6 years old)	
Healthy/	627	24 (mean 17 years old)	[258] (Bender MedSystems)
Cutaneous leishmaniasis	693 acute	41 (mean 20 years old)	
	1,003 non-healing	22 (mean 14 years old)	

Data with "(from figure)" mean that numbers were calculated from article's figures as they were not cited in the text. In the References column, the manufacturer of commercial ELISAs or non-commercial antibodies used for the concentration measurements are cited in order to comparison

WG Wegener's granulomatosis, *G* generalized, *CSS* Churg-Strauss syndrome, *MPA* microscopic polyangiitis, *PBC* primary biliary cirrhosis, *SCC* squamous cell carcinoma, *RA* rheumatoid arthritis, *MTX* methotrexate, *HAV, HBV, HCV* hepatitis virus, *EBV* Epstein-Barr virus, *ANCA* antineutrophil cytoplasmic antibodies

[a] Except where indicated

regulated secretion from cells upon fusion with the PM and have been particularly well studied within the immune system [208–210]. Exosomes with CD26/DPP-IV have been found in human saliva, released at the basolateral surface of enterocytes, and in ram epididymal fluid [211–213].

As it is not known to which CD26 functions regulation of this proteolytic or secretory process is related, the physiological role of soluble CD26 in biological fluids with respect to the transmembrane CD26 remains poorly understood. Current data support three potential biological functions for sCD26 refined in recent years, and which may be partly responsible for the different roles of CD26 in various clinical settings. (1) Involvement in the activation–deactivation of some chemokines and therefore in inflammatory processes. Extracellular proteases, many shed or ripped [30], which alter the chemokine gradients, participate in this crucial early step of the immune response. For CD26, the modulation of SDF-1 and the CXCR4 axis of cell homing has been particularly well studied [214, 215]. (2) Circulating sCD26 may also participate in the clipping or inactivation of the biologically still active blood substrates such as vascular regulatory peptides (substance P or bradykinin) [48], growth factors or hormones (e.g. 20% of incretins GLP-1 and GIP, originated in the gastrointestinal duct, are still active in the blood pool) [96, 97]. (3) In the case of oncogenic processes, in addition to possible involvement in both immunosuppressor [115, 177] and angiogenic mechanisms [48–56], the process of shedding may initiate or dampen the CD26 involvement in cell-adhesion processes through fibronectin, ADA or collagen binding, depending on its initial pro- or anti-oncogenic role in the tumourigenic niche or in a later metastatic process [110–114, 117, 118, 122, 127, 177].

Furthermore, sCD26 can participate in the immune response of T cell activation by APCs and CD86-dependent APC activation (CD86 is up-regulated in a caveolin-1/CD26 binding-dependent fashion), although this process should occur in the lymph node [13].

Other serum proteins with DPP-IV activity

The facts that around 10% of serum DPP-IV activity is not associated with sCD26 [2, 16, 187–189] and that CD26 gene knockouts or deficient animals still retain the same percentage of blood DPP-IV-like activity [43, 93, 216–218] suggest that other DASH proteins are present in systemic circulation.

DPP-II is possibly involved, as indicated by studies of enzymatic activity [175, 219, 220], although the use of preferential (but not specific) substrates and different pH (not fully discriminating) cannot prevent overlap amongst DPP-II, -IV or other DPPs [2, 16, 221, 222]. DPP-II/DPP7/QPP has a ubiquitous distribution and a limited range of substrates (tripeptides), and a housekeeping role in the final steps of peptide degradation in lysosomes has been suggested [221–224]. However, QPP has also been located in the cytoplasm and other non-lysosomal vesicules, it contains a leucine zipper motif that may endow it with extraenzymatic functions through protein–protein binding [225–227], and it may be involved in the apoptotic process [228, 229].

Although neither the physiological role of DPP-II nor whether it is secreted [230] have been elucidated

[221, 222], its intracellular activity is increased in squamous cell lung carcinoma [124], and varies with the progression of B-cell chronic lymphocytic leukaemia [231, 232]; moreover, its serum activity in patients with oral squamous cancer and hepatic cancer as well as in patients with lupus erythematosus and rheumatoid arthritis is higher than in healthy subjects [150, 233, 234].

FAP-α, which may form heterodimers with CD26, is also involved. Although it has a very restricted expression in normal human cells as a transmembrane protein [20–23], it has very recently been demonstrated that the circulating antiplasmin-cleaving enzyme (APCE) is a soluble derivative of FAP present in human plasma [235–237], and seprase activity (the other enzymatic specificity of FAP) has been purified from bovine plasma [238]. APCE circulating in human plasma appears to have a role in making α2AP (antiplasmin) more efficient for protection of extravascular fibrin, which forms as a host response to staunch haemorrhage [236]. However, although cultured endothelial cells have been reported to express FAP mRNA, translation of FAP protein was not documented [239], and the origin and additional functions of membrane-bound or soluble FAP under normal conditions remain enigmatic. Importantly, cancer patients probably have increased serum levels of this shortened form of FAP [20, 240].

Altered levels of serum sCD26/DPP-IV in diseases

By use of immunodetection, we have reported reduced levels of sCD26 in the serum of colorectal cancer (CRC) patients, compared with healthy donors, particularly in early stages of the disease, which suggested the potential usefulness of this molecule for early diagnosis of CRC [241, 242]. Later case-finding and case–control studies allowed us to obtain accurate clinical values that suggest that a serum CD26 test is an improvement on current non-invasive screening tests recommended for the detection of colorectal polyps and cancer [243]. Additional data [241–244] also support the usefulness of serum sCD26 levels for patient monitoring and prognosis. By use of an enzymatic activity assay, other authors found, however, increased DPP-IV activity in a similar cohort of colorectal cancer patients [245].

In the same way, in myocardial infarction patients treated with streptokinase, the concentration of enzyme is reduced to more than 50% after 90 days of therapy, while measurements of DPP-IV enzymatic activity did not change during that period [248].

On the contrary, the same authors found that there was no change in sCD26 concentrations but a lower enzymatic activity, with respect to the healthy donors, in rheumatoid arthritis and lupus erythematosus [92].

As mentioned above, these discrepancies can now be explained by putative changes in the glycosylation pattern (leading to a lack of immunorecognition of sCD26), the putative presence of DPP-IV activator attractin, or the secretion of DPP-II or, perhaps soluble FAP. These hypotheses require urgent research to validate sCD26/DPP-IV as a clinical marker.

As many studies have demonstrated altered serum levels of enzymatic DPP-IV activity (Tables 3, 4) and soluble CD26 protein (Table 2) in several diseases, the above factors should be taken into account. Although reference values of DPP-IV specific activity have been reported for serum (and plasma, with no difference) from a relevant group of healthy adults (Table 3) [2, 256, 261], most reports neither use the same assay conditions nor the same definition of specific activity, the same applies to the units of catalytic activity, making it difficult to compare these results, even from the same authors. In addition, some studies show contradictory results, probably related to the stage of disease considered (or a particular patient has been recruited) [92, 241–245, 249].

However, it is very interesting that the amount of sCD26 antigen found in normal serum with the most commonly used commercial ELISA kit (Bender MedSystems), corresponds well with the expected values based on the specific activity of purified serum DPP-IV [2, 256]. Together these findings support the use of immunodetection techniques for the quantification of these molecules because they are more specific.

We have included in Tables 2, 3 and 4 all major studies (if the disease is well represented, studies with all statistical groups of $n < 10$ are not included, although cited) published in English. Interestingly, many studies have used CD26 as a cell surface of Th1 cellular immune activation and sCD26 as a soluble marker, together with sCD30 and sometimes sCD23 as markers of Th2 (humoral response) [252, 253, 255, 257, 258]. Although there was no inverse correlation between increased sCD30 (see review [293]) and decreased sCD26 in many diseases, or vice versa, sCD30 is also shed (from hematopoietic cells) and, together with other surface antigens, it appear to suppress an appropriate T cell-dependent immune response, allowing tumour cells to escape immunosurveillance, resulting in progression of the tumour and spread of the disease [293]. It must also be remembered that DPP-IV activity has also been detected in other body fluids such as urine or synovial fluid, and its altered levels in some diseases has also been proposed as a clinically useful marker [273, 294].

The concentration of sCD26 increases in HIV-1 patients and leishmaniasis as well as in myocardial infarction and atopic dermatitis, does not change in asthmatics, osteoarthritis and gastric cancers, and decreases, apart from in CRC, in rheumatoid arthritis and particularly lupus erythematosus and Sjögren syndrome (Table 2). Results from hepatitis C virus (HCV) are not consistent.

Table 3 Studies showing physiological and pathophysiological levels of human serum (sometimes plasma) DPP-IV activity in patients with diseases not related to the immune response (type I diabetes is included for comparison) and with tumours

Disease	Catalytic activity/specific activity (±SD) (U L^{-1})[a]	Cohort (*n*)	References
Healthy	27.5 ± 6.1 women	481	[2, 259]
	32.3 ± 6.4 men		
Healthy	58 ± 16	64	[260]
Healthy/	22.6 ± 0.9	40	[261]
	21.8 ± 1.1	29 younger (<50)	
	24.1 ± 1.4	18 young male	
	18.2 ± 1.1	11 young female	
	24.5 ± 1.5	11 elder	
	23.8 ± 2.4	6 elderly male	
	25.4 ± 2.0	5 elderly female	
Gastric cancer	15.1 ± 1.1	27	
Pancreatic cancer	11.9 ± 2.8	2	
Gastric ulcer	17.4 ± 2.3	3	
Pancreatitis	21.0 ± 2.5	2	
Bile duct cancer	42.6 ± 10.5	2	
Acute hepatitis	37.4 ± 6.4	8	
Chronic hepatitis	33.4 ± 1.8	3 inactive	
	29.5 ± 4.2	5 active	
Cirrhosis	35.5 ± 3.6	11	
Healthy/	60.4 ± 3.2	12 males	[262]
Early hypertensive	81.0 ± 3.9	20 (without drug treatment)	
Fixed hypertensive	89.3 ± 3.7	17 (with drug treatment)	
Healthy/	51.6 ± 9.7	61	[263]
Umbilical blood	32.7 ± 5.9	65	
Gastric cancer	33.0 ± 7.8	9	
Blood cancers	38.8 ± 11.9	22 ALL	
	52.1 ± 24.11	62 AML	
	49.4 ± 23.7	28 CML	
	36.3 ± 5.6	11 lymphosarcoma	
	35.6 ± 11.6	5 Hodgkin's disease	
Healthy/	77.5 ± 17.1	100 (automated)	[264]
Hepatocellular carcinoma	198 ± 110.4	53 (+6 metastatic)	
Healthy/	70.1 ± 11.4	1,117	[265]
Gastric carcinoma	67.2 ± 20.4	10 early	
	51.1 ± 11.4	13 advanced	
Healthy/	43.9 ± 1.1	21	[266]
Miscellaneous cancers (<10 patients)	~32 (figure)	AML	
	~28 (figure)	ALL	
	~43 (figure)	CML	
	~31 (figure)	Malignant lymphoma	
	~32 (figure)	Multiple myeloma	
	~38 (figure)	Oesophagus	
	~28 (figure)	Colorectum	
	~48 (figure)	Liver	
	~43 (figure)	Gall bladder	
	~46 (figure)	Leiosarcoma	

Table 3 continued

Disease	Catalytic activity/specific activity (±SD) (U L^{-1})[a]	Cohort (*n*)	References
Healthy/	43.1 ± 4.8	45	[234]
Oral cancer (SCC)	28.6 ± 12.7	25	
Healthy/	55.1 ± 16.4	66	[267, 268]
Oral SCC	31.6 ± 12.4	51 (similar in all stages)	
Healthy/	11.6%A[b]	7	[215]
CTCL (NH lymphoma)	7.4	11 Sézary syndrome	
	8.6	7 mycosis fungoides	
Healthy/	54 ± 0.9	120	[270]
	54.1	60 men	
	57.7	30 younger (<50)	
	50.4	30 older	
	53.9	60 women	
	54	30 younger (<50)	
	53.8	30 older	
Osteoporotic	70.7 ± 1.8	30	
Healthy/	6.9 ± 1.4	10 infants	[273]
	5.9 ± 1.5	50 children	
	4.5 ± 1.5	50 adults	
Liver diseases	50.2 ± 12.2	7 Biliary atresia (paediatric)	
	9.4 ± 4.2 (GGT < 500)	8 Hepatitis syn. (paediatric)	
	36.9 ± 12.8 (GGT > 500)	8 Hepatitis syn. (paediatric)	
	6.5 ± 1.7	5 Jaundice pers. (paediatric)	
	17.1 ± 5.2	24 cirrhosis	
	25 ± 5.1	8 Mech icterus (tumour)	
	22.5 ± 4.8	6 Mech icterus (cholelith.)	
	13.6 ± 3.2	4 toxic liver	
	5.2 ± 1.1	5 chronic hepatitis	
	21.5 ± 9.4	23 primary biliary cirrhosis	
	28.1 ± 11.1	16 (primary biliary cirrhosis, late stages)	
Healthy/	12.4 ± 1.8	24	[275]
Liver diseases (PBC)	21.4 ± 1.8	42 (increases with stages)	
Healthy/	43.6 ± 10.6	17	[276]
Liver diseases (non-alcoholic steatohepatitis)	57.3 ± 7.8	31	
Healthy/	0.241 ± 0.015 (ΔOD/20 min)	9 (middle aged)	[277]
	0.223 ± 0.019	9 (elderly)	
Diabetes (II)/	0.179 ± 0.017	12 (middle aged)	
	0.173 ± 0.017	19 (elderly)	
Healthy/	34.5 ± 11.8	29	[278]
Diabetes (I)/	36.2 ± 11.7	29 medicated for years	
Diabetes (II)	27.7 ± 7.1	31 HbA_{1C} >8.5%; >1 year	
	22.1 ± 6.0	31 HbA_{1C} <7.5%; n. diag.	
	18.8 ± 8.8	31 IGT	
	~20 (figure)	62 NGT	

Data with "(figure)" mean that numbers were calculated from article's figures as they were not cited in the text

AML acute myelocytic leukaemia, *ALL* acute lymphocytic leukaemia, *CML* chronic myelocytic leukaemia, *CTCL* chronic T cell lymphoma, *HAV, HBV, HCV* hepatitis virus, *EBV* Epstein-Barr virus

[a] Except where indicated

[b] Absorbance

Table 4 Studies showing physiological human serum (sometimes plasma) DPP-IV activity and pathophysiological levels in patients with immune response related diseases (including psychologically related disorders)

Disease	Catalytic activity/specific activity (±SD) (U L^{-1})[a]	Cohort (*n*)	References
Osteoarthritis	~38 (figure)	26	[7]
Rheumatoid arthritis	~28 (figure)	41	
Healthy/	1.6 mmol/min mol (median)	25	[92]
Rheumatoid arthritis/	1.2 (median)	25	
Lupus erythematosus/	1.7 (median)	10	
Sjögren syndrome/	2 (median)	10	
Healthy/	41.3 ± 4.8	25	[269]
Rheumatoid arthritis/	34.5 ± 3.2	21	
Lupus erythematosus/	29.9 ± 64.6	21	
Healthy/	54 ± 0.9	120	[270]
Osteoporotic	54.1	60 men	
	57.7	30 younger (<50)	
	50.4	30 older	
	53.9	60 women	
	54	30 younger (<50)	
	53.8	30 older	
	70.7 ± 1.8	30	
Healthy/	~54 (figure)	22	[271]
Systemic lupus erythematosus	~43 (figure)	21 inactive disease	
	~39 (figure)	18 moderate disease	
	~37 (figure)	8 active disease	
Healthy/	9.3 ± 1.3	54	[249]
Systemic lupus erythematosus	5.8 ± 1.8	53	
Healthy/	0.95 ± 0.13 nmol/min/μg	79	[255]
HIV-1	0.82 ± 0.14	90	
Healthy/	0.77 ± 0.6	20	[272]
Sepsis	0.39 ± 0.15	15 moderate	
	0.26 ± 0.15	15 severe	
Healthy/	21.4(median)	12	[274]
Liver diseases	40 (median)	10 primary biliary cirrhosis	
	29.8 (median)	36 HCV	
	26.5 (median)	10 HBV	
	35.5 (median)	10 HAV	
	37.2 (median)	10 EBV	
Healthy/	71.9 ± 18.4	28	[279, 280]
Inflammatory bowel diseases	52.8 ± 16.9	63 Crohn's disease	
	55.7 ± 15.1	47 ulcerative colitis	
Healthy/	63.3 ± 15.1	28	[281]
Crohn's disease	55.8 ± 17.7	48 remission	
	47.1 ± 14.1	23 active	
Healthy/	~24 (figure)	10	[282]
Smokers	~18	9	

Table 4 continued

Disease	Catalytic activity/specific activity (±SD) (U L^{-1})[a]	Cohort (*n*)	References
Allergic asthmatics	~26	31 (do not change with corticoid therapy)	
Healthy breast-fed infants/	92.6 ± 4.8	13	[283]
Allergic (atopic dermatitis)	64.2 ± 13.2	23	
Healthy/	76.9 ± 23.1	50 children	[284]
Celiac disease (acute)	83.4 ± 20.2	48 children	
Healthy/	51.2 ± 15.6	52	[285]
Depression	49.2 ± 14.2	14	
Healthy/	40.8 ± 6.4	12	[285, 286]
Abstinent alcohol dependent	28.9 ± 7.3	12 (without liver damage)	
Stress	39 ± 7.7/38.8 ± 8.4 (after)	30	
Anxiety	37 ± 7.6 (changes in males)	22 (males and females)	
Healthy/	46.8	15	[287, 288]
Major depressed	36.9	36 (antidepressant resistant)	
Healthy/	19.4 ± 1.8	25	[289]
Major depressed	10.2 ± 1.1	18 (no change in additional 12 minor depressed)	
Healthy/	80.3	20 females	[290]
Hyporectic disorders	108.1	34 anorexia	
	91.1	11 bulimia	
Healthy/	34.4 ± 7.8	19 females	[291]
Hyporectic disorders	27.3 ± 14.7	21 anorexia	
	22.7 ± 11.4	21 bulimia	
Healthy/	29.4 ± 9.4	13 children	[292]
Tonsil diseases	39.8 ± 6.5 hypertrophy	19 before tonsillectomy	
	29.9 ± 7.3 hypertrophy	14 after tonsillectomy	
	19.9 ± 7.8	36 young adult	
	19.2 ± 2.7 recurring tonsillitis	13 before tonsillectomy	
	12.7 ± 5.2 recurring tonsillitis	8 after tonsillectomy	

Data with "(figure)" mean that numbers were calculated from figures in the article because they were absent from the text

RA rheumatoid arthritis; *HAV, HBV, HCV* hepatitis virus; *EBV* Epstein-Barr virus

[a] Except where indicated

DPP-IV enzymatic activity is high in patients with hepatic cancer, hepatitis, osteoporosis (in which it probably determines the severity of the disease), cholestasis and other liver diseases (Table 3), and in psychologically related eating disorders such as anorexia or bulimia (Table 4). In contrast with protein levels, it is also increased in CRC, rheumatoid arthritis, lupus erythematosus and Sjögren syndrome, according to some studies and in disagreement with others [92, 241–245, 249, 295, 296]. DPP-IV levels remain unchanged in metastatic bone disease, oesophagus, gall bladder, chronic myelocytic leukaemia or leiomyosarcoma cancers (Table 3), and in allergic asthma (with or without treatment with inhaled glucocorticoids, although it changes in allergic infants) and in celiac disease (Table 4). In adult T cell leukaemia, although serum DPP-IV is strongly correlated with the percentage of CD26+ T cells, no apparent change in the mean value of activity was found [297]. However, decreased levels of DPP-IV are observed in patients with some blood (particularly acute lymphocytic leukaemia), thyroid [298] and oral cancer, advanced gastric carcinoma, and in particular, colorectal cancer (in accordance with our data) (Table 3). Lower levels were also found in HCV infections, in inflammatory bowel diseases, in healthy smokers, in pregnancy [299] and in type II diabetes, and in alcoholics and patients suffering from major depression. A reduction in DPP-IV activity has been related to symptoms of depression and anxiety under certain circumstances, with contradictory results in bulimia and anorexia (Table 4).

In summary, low levels of DPP-IV/sCD26 occur concurrently with impaired immune status, including some haematological and solid malignancies, whereas increased

levels occur in inflammatory and infectious diseases (enhanced immune status), other haematological tumours, and liver diseases.

The source of sCD26

In order to validate a candidate clinical or tumour marker, or a therapeutic target, it is important to know how it is distributed in cells, tissues or systems, as well as the circumstances that provoke its abnormal presence/absence. However, the origin of serum CD26 is unknown.

The hepatobiliary system was the first to be suggested as the sCD26 source by the group of Nagatsu [261] because serum enzyme activity levels in hepatitis and cirrhosis patients were correlated with the serum group of enzymes that are present at high levels in patients with obstructive jaundice and infiltrative disease of the liver. However, they were cautious because electrophoresis revealed the presence of novel isoforms in the sera from those patients, and lower activities in patients suffering from gastric or pancreatic cancer and normal levels in patients with pancreatitis were observed. Liver epithelium is often cited as the most likely potential source of serum CD26 as hypothesized from hepatocellular carcinoma studies, in which loss of CD26 from membrane is accompanied by increased DPP-IV activity in patients [106, 107, 116, 264, 273], and similar results were also observed in studies of hepatic regeneration [14, 300, 301]. However, the increased enzyme activity could not be explained by CD26 expressed in hepatocytes [14], and CD26 is predominantly located in the bile canaliculi [273, 275, 302]. At least in some conditions, sCD26 originates from the brush border of hepatocytes [273], but a recent study found that in chronic hepatitis C and other liver viral infections DPP-IV activity levels were not correlated with several markers of bile duct injury or hepatocyte injury [274]. The authors, therefore, suggested that the increased activity in these diseases may originate directly from shedding from the peripheral blood T cells involved in the control of viral infections or, in the case of HCV infection which takes place with a weak T cell response during the chronic phase of the disease, indirectly by stimulating other cells such as hepatic stellate cells. The involvement of T cells in the enhancement of sCD26 levels has already been suggested by the group of Gorrell and McCaughan [14, 303] in studies of liver regeneration, where T cell activation is known to occur.

Interestingly, the events observed in hepatocarcinoma—loss of membrane CD26 and elevation of DPP-IV levels—are not seen in CRC. Almost all CRC patients show reduced serum levels of sCD26 [241–243], whereas loss of membrane CD26 expression only occurs in 11% of colorectal tumours [108], i.e. in CRC, sCD26 is not correlated with cell proliferation, or with the alteration of CD26 expression in CRC tumour cells. There is no direct correlation between sCD26 levels and tumour location, degree of histological differentiation, type of metastasis or Dukes' stages of CRC [241], which may affect the hepatic production of sCD26. As in hepatic regeneration but in the opposite direction, immunity involved in CRC as an immune defective anti-tumour response, including a deficiency in IL-12 production [304] which is a well-known CD26 up-regulator in T lymphocytes [305], has been described.

A possible origin of sCD26 from the immune system, as well as from spleen, was first suggested in 1984 by Kasahara et al. [306], as these authors observed a significant correlation between the normal serum DPP-IV activity and the peripheral blood lymphocyte count, although they also identified serum isoforms from liver, spleen or kidney. Kidney, an obvious potential source because it contains large amounts of CD26, was rejected early on [187] because anephric individuals have normal amounts of sCD26, and because sCD26 contains approximately twice as much sialic acid as kidney CD26.

Several data suggest that serum CD26 is at least partly shed from T cells. Much data come from glycosylation and electrophoretic mobility studies. The sialylation of CD26 appears to be cell-type specific: the sialic acid content of vascular and circulating CD26 is higher than that of the kidney and intestinal brush border enzyme [85, 307, 308]. Sialylation of CD26 is increased in peripheral blood mononuclear cells (PBMCs) of healthy elderly individuals (by 80 years of age, sialylation of T cell DPP-IV/CD26 is three to five times that of a healthy 20-year old); hypersialylation is more extreme in HIV-positive individuals with AIDS, and these glycosylation states coincide with the forms found in the corresponding serums [178]. Sialylation may prevent removal from the circulation by the liver asialoglycoprotein receptors and increased sialylation may be related to impaired immunocompetence [92, 178, 307, 308]. However, these data do not preclude the possibility of sCD26 shed being from the endothelium of venules or the capillary bed of several organs such as lung, myocardium and striated muscles, spleen and pancreas [3, 201, 202, 307, 309–313].

Other data include the changes in sCD26 levels in relation to physiological or pathophysiological processes. As already commented, most changes (Tables 2, 3, 4) occur concurrently with the immune status, sCD26 levels decrease generally in disease unless a liver injury or extensive lymphocyte proliferation is involved [2, 11–14]. In relation to this, reduced concentrations of the peptidase in healthy smokers, alcoholics and severely depressed patients (Table 2) are consistent with impaired immune response. Interestingly, anti-TNFα treatment (adalimumab) of patients with rheumatoid arthritis augmented DPP-IV activity [314]. Also, that sCD26 may be valuable as prognostic marker in

CRC [241] fit this hypothesis, because patients with activated immune systems (higher sCD26 levels) may show a better chance of survival than those with lower sCD26 levels.

The most important data correspond firstly to in vitro studies [305, 312, 315, 316] which demonstrate secretion/shedding of sCD26 from lymphocytes to culture media, whereas no data exist for other cell types; interestingly, TGF-β_1 down-regulates CD26/DPP-IV expression in T cells, which is accompanied by decreased DPP-IV activities in the supernatants of cultured cells [316]. Secondly, many in vivo studies found a correlation between changes in serum DPP-IV activity and the numbers of PBL, T lymphocytes, CD26+ T cells and the amount of CD26 in T lymphocyte plasma membranes, in patients with adult T cell leukaemia [297], oral cancer [315], gastric and colorectal carcinoma [317–319], with mycosis fungoides and Sézary syndrome (two major variants of the cutaneous T cell lymphoma, a type of non-Hodgkin lymphoma) [215], with the autoimmune diseases systemic lupus erythematosus [271], with arthritis rheumatoid [247, 249, 306] and inflammatory bowel (Crohn's disease and ulcerative colitis) [279, 281], with adult allergic asthmatics [251] and in human miscarriage [320]. In addition, cell surface CD26 [88, 305, 321–326] and serum sCD26 are markers of Th1 cellular immune activation together with CD30 and sCD30 as markers of Th2 (humoral) response, although an inverse correlation between increases in sCD30 and decreases in sCD26 or vice versa was not always found in diseases, as already mentioned [252, 253, 255, 257, 258, 293, 327–332].

Although these changes in cell surface and soluble forms may be associated with regulation of the enzymatic cleavage of CD26 from the T cell surface, the observation of anti-CD26 autoantibodies in rheumatoid arthritis and systemic lupus erythematosus patients and the fact that its levels are correlated with an increased clearance rate of the circulating CD26 [92, 248] suggest an alternative, but also immune-related, hypothesis for the regulation of sCD26 levels. It will be interesting to look for these autoantibodies in cancer patients to test this hypothesis. In fact, an association between chronic inflammatory conditions and eventual development of cancer was described several years ago [333, 334].

In summary, a fraction of serum CD26 originates from immune system cells, and this sCD26 fraction can be regulated and, therefore, causes an imbalance amongst specific sCD26 isoforms in the serum of patients.

On the role of sCD26 in cancer: conclusion

Complex crosstalk between the lymphoid lineage and malignant tumours in vivo has been discussed since the days of Paul Ehrlich a century ago; the ability to suppress the immune response is essential for tumours to develop [116, 174, 333–336]. Taking the example of CRC and the lower levels of sCD26 in these patients, we will suggest a framework to research the hypothetic role of sCD26 in crosstalk between the immune system and carcinogenesis. This should be investigated because drugs that inhibit DPP-IV activity [96–98, 101–104] may exacerbate development of tumours and/or immune diseases and, consequently, a follow-up of diabetics under this therapy should be done. In a similar way, it has been already proposed that genetic or environmental factors that decrease DPP-IV activity might increase the risk of ACE (angiotensin converting enzyme) inhibitor-associated angioedema [43, 337].

It is well known that tumour cells secrete immunosuppressive factors such as TGF-β_1. TGF-β_1 acts on many immune cells such as APCs, T cells and NKT cells, thus participating in the induction of T tolerance to tumour antigens [174, 338], and down-regulates in vitro CD26/DPP-IV expression in T cells as well as culture supernatant sCD26 levels [316]. Consequently, it is possible that TGF-β_1 also down-regulates production of circulating sCD26 in cancer patients, which may reflect tumour-induced T cell tolerance (Fig. 1). The facts that inhibitors of CD26/DPP-IV activity up-regulate TGF-β_1 secretion by T cells in vivo [172, 175], that anti-TNF-α therapy augments DPP-IV activity in patients with rheumatoid arthritis [314] (TNF-α is pivotal in inflammatory reactions and is frequently detected in human cancers), and that an immune defective IL-12 production (a well-known CD26 up-regulator [17, 204, 305] has been described in CRC [304] also support this link.

By lowering CD26 expression, sCD26 and therefore the DPP-IV activity, tumour cells will alter one or more of the physiological functions of that protein. For example, immune cell homing through chemokine clipping, as already mentioned (Table 1) [11], i.e. accumulation of plasmacytoid dendritic cells found inside ovarian and head and neck SCC, was attributed to SDF-1/CXCL12 secreted by malignant cells [339, 340]; also, Tregs were recruited to the tumour site under the influence of CCL22 [341]. Another consequence may be to increase the active levels of incretins GLP-1, -2 and GIP, and in doing so, to improve insulin secretion. This argument has already been used by Meneilly et al. to explain the lower DPP-IV levels in elderly obese patients with diabetes as an adaptation of the body to enhance the incretin-mediated insulin secretion [241]. A diverse body of evidence that relates higher levels of insulin to elevated risk of colon cancer and carcinogenesis in general, through direct and/or IGF-1-dependent mechanisms, has been impressively reviewed [342]. Moreover, GLP-2 has direct tumour-promoting effects on intestinal cancer cells (and perhaps it may be generalized to other cancers) [343].

Therefore, the lymphocyte count, subset distribution and other immune parameters of patients, as well as the levels of entero- and neuropeptides, should be recorded in future studies of CRC and other carcinomas. As suggested in a study with rats [344], in which the antidiabetic agents metformin and pioglitazone (that improve insulin sensitivity) reduced serum DPP-IV activity, in direct relation to reductions in glycosylated haemoglobin and increases in GLP-1 levels, it should be investigated whether glycemic control regulates the release of DPP-IV from the different cell types proposed as its source; the isoform patterns of sCD26 and CD26 in those tissues should also be studied. In vitro and in vivo studies also showed cyclosporin A down-regulation of CD26 and sCD26 [204, 345].

DPP-IV is also an important regulator of NPY-induced angiogenesis in the Ewing's sarcoma family of tumours [54–56], and can be up-regulated by hypoxia in endothelial cells [346]. This up-regulation may explain the increased levels of the protein and the poorer behaviour of sCD26 as a marker, in late-stage CRC Duke's D patients (and tumour angiogenesis) with respect to earlier stages [241]. However, the effect of pathophysiologically lower sCD26 concentrations on the NPY-YRs system, including vasoconstriction, is not known [347].

Another important feature, in relation to the value of sCD26 as a biomarker, is the timing of sCD26 alterations in the plasma of patients with tumours and/or immune system-related diseases. If further studies confirm this hypothetic immunosuppressive mechanism mediated by tumour cells (Fig. 1), then they would have identified another target to be used to overcome immunological tolerance and promote tumour regression in combination with other conventional strategies.

Current clinical trials (basically vaccination strategies and adoptive transfer of effector cells) aimed at harnessing the immune system to eliminate tumours already include sometimes immunomodulatory agents that support Th1 responses, such as IL-2, -12, -18, -21, and IFN-γ [348–352], which may enhance the sCD26 levels [252, 253, 255, 258, 259, 293, 327–332]. The effectiveness of anti-tumour responses is usually restricted by inhibitory signals from the tumour microenvironment, and some progress has been made in the direction to combining strategies involving blockade of these signals [175, 348]. Anti-TGF-β treatment should also lead to higher sCD26 levels [173, 176, 316]. Treatment with high exogenous concentration of TNF has some anti-tumour effects but TNF produced endogenously, by several types of tumour cells (including colorectal) and by many immunotherapy treatments that induce higher levels of TNF, also favours the development and progression of cancer [353]. Therefore, the use of anti-TNF therapy has been proposed for cancer therapy and employed in some clinical trials, with no need to avoid TNF administration in cases of organ-confined solid tumours, if required [348, 354]. Millions of patients with autoimmune/inflammatory disorders have been treated with antibodies against TNF, which enhance sCD26 levels [314]. In conclusion, the proposed immunosuppressive mechanism may be easily short circuited by a combination of stimulatory therapy, anti-TGF-β and anti-TNF treatment.

Finally, sCD26 levels are higher in patients at late and metastatic stages [241, 275] as well as in patients with liver tumours in general and other liver diseases [261, 264, 266, 273, 276]. Consequently, drugs that inhibit DPP-IV activity or anti-CD26 Ab [153] may be helpful in these cases.

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