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CD26 and Asthma: a Comprehensive Review

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Abstract Asthma is a heterogeneous and chronic inflammatory family of disorders of the airways with increasing prevalence that results in recurrent and reversible bronchial obstruction and expiratory airflow limitation. These diseases arise from the interaction between environmental and genetic factors, which collaborate to cause increased susceptibility and severity. Many asthma susceptibility genes are linked to the immune system or encode enzymes like metalloproteases (e.g., ADAM-33) or serine proteases. The S9 family of serine proteases (prolyl oligopeptidases) is capable to process peptide bonds adjacent to proline, a kind of cleavage-resistant peptide bonds present in many growth factors, chemokines or cytokines that are important for asthma. Curiously, two serine proteases within the S9 family encoded by genes located on chromosome 2 appear to have a role in asthma: CD26/dipeptidyl peptidase 4 (DPP4) and DPP10. The aim of this review is to summarize the current knowledge about CD26 and to provide a structured overview of the numerous functions and implications that this versatile enzyme could have in this disease, especially after the detection of some secondary effects (e.g., viral nasopharyngitis) in type II diabetes mellitus patients (a subset with a certain risk of developing obesity-related asthma) upon CD26 inhibitory therapy.

Keywords CD26 · DPP4 · Asthma · Cytokines and chemokines · sCD26 · CD26 inhibitors

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Definition and Genetic Factors Implicated in Asthma

Asthma is a heterogeneous and chronic disease characterized by reversible expiratory airflow limitation, bronchial hyperresponsiveness, mucous cell hyperplasia, higher vasculature permeability, airway remodelling with fibrosis and inflammatory cell infiltration [1, 2]. Asthma is a major concern, with 334 million people worldwide affected, increasing prevalence [3] and a high economic charge [4]. It is more frequent and severe in boys until the age of 13 years, but both prevalence and severity of asthma rise in women after puberty, becoming even more prevalent in females [3, 5, 6]. Five to 10 % of cases display a highly severe and treatment-refractory disease, suffering from recurrent exacerbations that threaten a patient's life and increase the healthcare costs. This is a complex pathology, with both genetic and environmental factors causing increased susceptibility and severity. Great efforts have been made to discover the genetic bases (mostly genome-wide association studies in asthma (GWAS)), revealing the influence of several genes encoding proteins with an important role in the immune system (HLA-DQ, HLA-G, IL1RL1, IL18R, TSLP, PDE, IL-33, LRRC32, SMAD3, IL2RB, IL6R, IL-13) and also proteases (ADAM33 and dipeptidyl peptidase 10 (DPP10)) [7–9].

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Asthma and the Prolyl Oligopeptidase Family of Proteases: Dipeptidyl Peptidase 10 and CD26/DPP4

As commented above, proteases are involved in many physiological and pathological processes, including chronic respiratory conditions like asthma. Amongst all proteases, there are only a few proline-specific enzymes, as peptide bonds adjacent to proline (present in some growth factors, chemokines or cytokines) are resistant to cleavage [10]. These enzymes include serine proteases, with a serine residue in their catalytic region (sequence consensus Gly-Xaa-Ser-Xaa-Gly) [11] and covering different families (S1–S81) and subfamilies. Thus, the S9 family (prolyl oligopeptidases) includes from S9A to S9D, all with the catalytic triad Ser, Asp, His but with slightly different sequence consensus around the catalytic Ser. For example, most of the members of the S9B subfamily (EC 3.4.14.5; CD26/DPP4, DPP8, DPP9 and fibroblast activation protein/FAP/Seprase) (http://merops.sanger.ac.uk/) present the sequence Gly-Trp-Ser-Tyr-Gly-Gly, while the other additional two members, DPP6 (DPPX; Gly-Lys-Asp-Tyr-Gly-Gly) and DPP10 (Gly-Lys-Gly-Tyr-Gly-Gly), do not possess the catalytic serine and, therefore, DPP4 activity [12]. Curiously, four of these peptidases (CD26, FAP, DPP6, and DPP10) are type II membrane proteins released to the extracellular medium, three are encoded by genes located on chromosome 2 (CD26, FAP and DPP10) and only two (CD26, DPP10) appear to have a role in asthma [13–16]. For example, DPP10 has been linked to asthma susceptibility in different populations [7, 13, 15], and this protein (as well as DPP8 and DPP9) has been primarily located in the trachea and the bronchi of the airways in rats [17]. For its part, the protease CD26 is the major member of the S9B family and also a receptor for the Middle East respiratory syndrome coronavirus (MERS-CoV) [18, 19], a new coronavirus that causes severe lower respiratory tract infections that could lead to asthma exacerbations. CD26 has been found elevated in both plasma samples (soluble CD26 or sCD26) and the surface of peripheral $CD4^+$ T cells from adult patients with allergic asthma [20, 21], and different animal models [14, 16, 22] suggest a role of this peptidase in the pathogenesis of this disease.

Structure and Distribution of CD26

Structure of the CD26 Molecule

CD26 is a single-pass type II integral membrane glycoprotein of 105–110 kDa [23]. Only the homodimeric form of CD26 is biologically active [24–27]. Homodimerization takes place in both the Golgi apparatus [28] and the endoplasmic reticulum [29]. Each monomer displays a highly conserved and short (six amino acids) cytoplasmic tail at the *N*-terminus, a 22-amino acid hydrophobic transmembrane region and a long extracellular domain of 738 amino acids. The heavily *N*-glycosylated extracellular domain can be subdivided, in turn, in several regions. The closest to the amino terminal part starts with a flexible stalk region and contains 8 out of 10 possible *N*-glycosylation sites, while the intermediate region is highly enriched in cysteines (9 out of 12). Finally, the active centre is located towards the carboxyl-terminal end and is another highly conserved region [30–34].

Tissue and Cell Distributions of CD26

Human CD26 is broadly distributed in a variety of cell types, tissues and organs [35–39]. Lungs display the second highest CD26 activity amongst organs, especially in lung parenchyma [17, 22]. Contrary to DPP8/9 and DPP10, bronchi almost do not express CD26 [17], but it can be found in the apical membrane of epithelial cells, capillary endothelial cells, fibroblasts and serosal submucosal glands of human bronchi [40–42]. In most of these places, CD26 levels are constitutive and highly correlated with the messenger RNA (mRNA) content (http://www.proteinatlas.org/ENSG00000197635-DPP4/tissue) [43]. However, IL-13 causes a strong proinflammatory upregulation of CD26 in the airway epithelial cells [44]. Moreover, both DPP4 activity and CD26 protein (but not mRNA) increase after allergen exposure in lung parenchyma in a rat model of allergic airway inflammation [17], suggesting that CD26 on lung epithelium could be important in asthma pathogenesis [45].

CD26 is also expressed in the immune system, being detected in medullar thymocytes, T cell areas of spleen and lymph nodes, peripheral blood T cells and, at a lesser extent, B cells, NK cells, monocytes/macrophages and granulocytes [24, 25, 30, 41, 46, 47]. CD26 density in these cells is heavily controlled and augments upon cell activation and acquisition of a memory phenotype, especially in the T cell lineage [33, 41, 48]. Human T lymphocytes display variable basal expressions of CD26 ($CD4^+$ T >> $CD8^+$ T cells), which depends on the individual and the mAb used. Despite that not all resting T cells are $CD26^+$, most of them contain CD26 mRNA and display CD26 molecules on the surface 4–8 h after stimulation [49–51]. However, only a certain regulation on CD26 mRNA levels has been detected by either northern blot [36, 50, 52–54] or gene arrays [55] upon activation. Additionally, CD26 is upregulated by interferon gamma (IFNγ) on renal epithelial cells [56] and B-CLL [57] through the modification of mRNA levels.

Despite the above described adjustment of CD26 expression through mRNA levels, several evidences support the presence of upstream control levels. Thus, CD26 is strongly regulated at protein level by several soluble factors. For

example, the T_{H1} cytokine IL-12 (and to a lesser extent IL-2) enhances the expression of CD26 on both activated T cells [58, 59] and NK cells (together with IL-15) [47, 60]. On the contrary, IFNγ (another T_{H1} cytokine) has no effect on CD26 levels in these lymphocytes [47, 58]. Regarding T_{H2} cytokines, IL-4 promotes the expression of CD26 on human B lymphocytes activated with *Staphylococcus aureus* Cowan I [61, 62], while this cytokine moves from a lack of effect [63] to a certain downmodulation of CD26 levels in T cells at high concentrations [unpublished results]. In addition, in vitro exposure to regulatory T cell (Treg)-derived soluble factors like transforming growth factor beta 1 (TGF-β1) [64, 65] or adenosine (Ado) [66] leads to diminished CD26 levels.

Most of peripheral blood Treg lymphocytes display an "activated-like" (e.g., $CD25^{high}$), "memory" ($CD45RO^{+}$) and an "anergic/apoptosis-prone" phenotype [67] and were expected to express other activation/memory markers such as CD26. This seems to be the case for rats, where $CD25^{+}$ (Treg) and $CD25^{-}$ (effector T cells or Teff) subsets of peripheral $CD4^{+}$ T cells show equivalent CD26 expression [68]. In contrast, human Treg cells ($CD4^{+}CD25^{high}$ or $CD4^{+}FoxP3^{high}$) display lower levels of CD26 compared to Teff lymphocytes ($CD4^{+}CD25^{-/low}$ or $CD4^{+}FoxP3^{-/low}$) [69–72]. This likely explains why cytokines that favour "effector" responses (e.g., IL-12) cause a strong upregulation of CD26 on "bulk" T_{H} cell cultures, while others important for the Treg homeostasis (e.g., IL-2, IL-15) only induce a slight increase on CD26 levels [58, 73]. It also gives a clue on why CD26 is downmodulated upon exposure of T cells to TGF-β1 [64, 65].

CD26 expression amongst Teff lymphocytes is also variable, and T_{H17} cells appear to display the highest levels of CD26 according to the following order: $T_{H17} >> T_{H1} > T_{H2}$ [72, 74–77]. Furthermore, two subsets were reported amongst T_{H17} cells on the base of CCR4 expression [78], but only the $CCR4^{-}$ T_{H17} subset (and not the TGF-β-secreting $CCR4^{+}$ T_{H17} subpopulation) has a $CD26^{high}$ phenotype [79]. This finding likely indicates that the degree of phenotypic diversity found in Teff cells for CD26 levels is also probably present in Tregs and reflects the presence of functionally different subsets that mirror the corresponding Teff subsets [80].

The different expression levels of CD26 in Treg and Teff lymphocytes could depend on a variation in CD26 mRNA levels, like it happens with "regulatory-like" $CD4^{+}$ T cells in classical Hodgkin's lymphoma [81]. However, it is worth to mention that, apart from regulating this set of CD26 mRNA molecules, there is an intracellular pool of CD26 protein maintained by continuous translation in human T cells (regardless of their $CD26^{+}$ or $CD26^{-}$ phenotype) [50] that can be mobilized towards the plasma membrane [54] or released into the extracellular space. Therefore, there could be a number of additional mechanisms leading to a $CD26^{-/low}$ phenotype in human Treg cells.

Body Fluid Compartments and Distribution of Soluble CD26

CD26 can be found in the extracellular space, with autocrine, paracrine or endocrine effects. The soluble version of CD26 (sCD26) has been described in many biological fluids (e.g., serum, plasma, synovial fluid, cerebrospinal fluid) from different organisms [82]. Bronchoalveolar lavage contains DPP4 enzymatic activity in rats [17] and humans [83]. In serum or plasma, at least 90 % of this activity is associated to a heavily glycosylated 110-kDa CD26 isoform [84, 85], whose concentration displays a normal distribution [86] and high biological variability [87, 88] that seems to depend on pre-analytical variables, like age or gender. Thus, serum sCD26 concentration increased up to 10–12 years in children, after which the values start decreasing [89]. In adults, a slight decrease of sCD26 or DPP4 activity in serum with age has been also detected [87, 88], but other studies did not describe such correlation [86, 90]. In addition, no differences were detected regarding gender in some studies [90], while different authors did find a higher sCD26 concentration in serum/plasma samples [86–89, 91] but a lower CD26 expression on $CD4^{+}$ T cells (our unpublished results) from males.

Several studies have found a positive correlation between sDPP4 activity and sCD26 in humans [91–93], but others have reported a low correlation instead, with different explanations like the presence of hypersialylated CD26 isoforms or alternative proteins with DPP4 activity [82]. Thus, plasma samples contain a soluble glycoprotein named DPPT-L or attractin without homology with CD26 but with DPP4 activity [94–96], although this activity has been questioned more recently [97]. Attractin is accumulated in the plasma membrane upon T cell receptor (TCR) triggering (~24 h) [95, 96], especially in $CD26^{high}$ Teff cells (our unpublished results), and released into the plasma at 48–72 h [95, 96]. Curiously, linkage disequilibrium studies show association of asthma with a region including the attractin (ATRN) gene, which is upstream of the gene encoding the secretase/sheddase ADAM-33 (an asthma susceptibility gene) [97].

Release of CD26 could be accomplished by a classical or non-classical pathway and either by a constitutive or induced mechanism. The classical pathway requires vesicular traffic from the endoplasmic reticulum/Golgi towards the plasma membrane. Intravesicular proteins are liberated in the extracellular medium after membranes merge (exocytosis), while transmembrane proteins appear in the secretome through proteolysis mediated by "secretases"/"sheddases". This last process ("shedding") delivers growth factors, cytokines, receptors and probably molecules like CD26 [98]. This is additionally supported by the lack of posttranscriptional splicing in CD26 mRNA, the absence of cytoplasmic and transmembrane domains in sCD26 or results from pulse chase and transfection experiments [25, 82]. However, CD26 has been detected in microvesicles and exosomes from lymphocytes

(http://www.exocarta.org). Therefore, constitutive or induced release of $CD26^+$ vesicles (exosomes, microvesicles or apoptotic bodies) into the medium could also contribute to the pool of sCD26 in the circulation and reflect the cell subset of origin ("cell lineage fingerprint").

The cell source of sCD26 is still controversial [25, 82]. Visceral fat, at least in obese patients, overexpresses CD26 and releases this "adipokine" into the circulation [88], and there are data supporting the presence of a positive correlation between fasting sCD26 levels and body mass indexes (BMIs) >25 [88, 99]. Soluble CD26 may also originate from other sources, such as endothelial cells (e.g., lung) or epithelial cells from liver (bile canaliculi) or kidney. However, immune cells are also a likely source [25, 82, 100]. Thus, a transplantation model in rats has determined that, under healthy conditions, bone marrow-derived cells represent a significant source for sCD26 [101]. Therefore, the concentration of sCD26 could also be influenced by the number of lymphocytes [102] or mirror the predominant phenotype of circulating $CD4^+$ T lymphocytes in a pathological situation.

CD26 and Asthma

Asthma Phenotypes, Disease Severity and CD26 levels in $CD4^+$ T Cells

$CD4^+$ T_H cells play a central role in adaptive immune responses and the induction/persistence of asthma and other allergic/atopic diseases. They are plastic and heterogeneous lymphocytes, with four main lineages (T_{H1}, T_{H2}, T_{H17} and Treg cells) and different roles. For example, T_{H2} (GATA-3^+) cells infiltrate airways in allergic asthma and produce a set of cytokines (IL-4, IL-5, IL-13) important for airway remodelling, leucocytosis, eosinophilia, macrophage/mast cell activation and B cell-dependent IgE elevation [103, 104]. In the same way that T_H lymphocytes are heterogeneous, there are also a number of asthma phenotypes as a likely reflection of the T_H cell heterogeneity itself, with both T_{H2}^{high} and T_{H2}^{low} phenotypes sharing different clinical signs: (a) the *early allergic asthma*, with a strong familiar background and mediated by T_{H2} cytokines (T_{H2}^{high}) and allergen-specific IgE (atopy); (b) the less-allergic *late-onset asthma* (T_{H2}^{high}), which is characterized by eosinophilic inflammation, absence of specific IgE (i.e., non-atopic) and worse response to corticosteroids; (c) the *neutrophilic asthma*, a T_{H2}^{low} phenotype refractory to corticosteroids and linked to T_{H17} responses, sputum neutrophilia and augmented levels of IL-8 and IL-17; (d) and the *obesity-related asthma*, a T_{H2}^{low} phenotype predominant in obese women, with higher levels of tumor necrosis factor alpha (TNFα), IL-6 and leptin but low numbers of eosinophils [1] (Table 1). Therefore, alternative $CD26^{+/high}$ effector T_H subpopulations are gaining importance in asthma, particularly as disease becomes chronic and refractory to treatment. In this context, even though it was initially described that $CD26^+$ T_{H1} cells were protective ("hygiene hypothesis"), now it is considered that these cells could be favouring the inflammation of the airways [105]. In addition,

Table 1 Asthma: molecular and clinical classification

	Symptomatology and pathophysiology	Pathobiology	Therapy response
Th2-high phenotype			
Early onset Allergic	Allergic and rhinitis symptoms Moderate to severe	Elevated levels of IL-4, IL-5 and IL-13 (Th2-related chemokines), specific IgE and thicker subepithelial basement membrane	Corticosteroid response and Th2-related targets
Late onset Eosinophilic	Presence of sinusitis and less allergic Normally severe	Eosinophilia and IL-5 elevation (Th2-related chemokine)	Against IL-5-Ab response and to cysteinyl leukotriene modifiers. Refractory to corticosteroids
Th2-low phenotype			
Obesity-related	Mostly women, very symptomatic, epithelial hyperresponsiveness	Loss of Th2-markers and oxidative stress	Response to weight loss, to antioxidants and to hormonal therapy
Late onset Neutrophilic	Low FEV1	Sputum neutrophilia, Th17 and IL-8 ways	Refractory to corticosteroids and to other asthma medicines Possibly response to macrolide antibiotics

Modified table from Martinez et al. [9]

IL-5 interleukin 5, *IL-8* interleukin 8, *FEV1* forced expiratory volume in 1 s, *Ab* antibody

proinflammatory CD26^{high} T_{H17} cells have been detected in biopsies from asthma patients and their cytokines (e.g., IL-17, IL-6, IL-21, IL-22) are involved in eosinophilia/neutrophilia and higher severity during acute attacks [106]. On the other hand, Treg cells (FoxP3^{+}, CD26$^{-/low}$) also seem to play a relevant role in controlling exaggerated T_{H2} responses and asthma development [9, 107, 108]. Treg cells exert their suppressor activity by using both soluble (e.g., adenosine, TGF-β, IL-10) and membrane-associated (e.g., TGF-β, CTLA-4) molecules [67], and a number of GWAS in asthma have identified some genes (e.g., IL2RB, SMAD3, GARP/LRRC32) linked to this suppressor activity. Thus, the lower or higher prevalence of different Teff subsets and/or the distortion of the Teff/Treg balance could also alter the phenotype and severity of asthma [104, 109, 110]. Moreover, depending on the asthma phenotype or the severity of this disease, the levels and functions of CD26 on the surface of immune cells and biofluids could be rather different and be a factor influencing disease development. Therefore, it is time to ask what the biological functions of CD26 are and what their connection with asthma is.

Enhancing Functions of Both Membrane and Soluble CD26 on Asthma

Functionally speaking, CD26 is a complex molecule with both harmful and beneficial activities in relation to asthma. With regard to the first ones, CD26 has been traditionally linked to both the amplification of TCR-mediated stimulatory signals and cell adhesion/migration. These functions could be dependent on production of certain biomolecules, the enzymatic activity of CD26 or the extracellular association with other proteins: adenosine deaminase (ADA) [111], CD45 [112], caveolin-1 [113], CXCR4 [114], collagen [115], plasminogen 2 [116], glypican-3 [117] or fibronectin III [118, 119] (Fig. 1). For example, CD26-mediated costimulation plays a role in the migration of mesothelioma cells through upregulated production of a current biomarker of "T_{H2}^{high}" asthma: periostin [120, 121]. CD26 location could also be important for this harmful function of CD26 in asthma. As a raft resident protein [112, 122], CD26 improves the immunological synapse formation between antigen-presenting cells (APCs) and T cells [112, 113], important for T_H cell proliferation/differentiation and to empower these lymphocytes to proportionate help to B cells and produce immunoglobulins like IgE [30] (Fig. 1). This raft-dependent costimulatory function of CD26 could be mediated by other proteins like CD45, a tyrosine phosphatase (PTPase) essential for TCR signalling [123]. Cross-linking with anti-CD26 antibodies in T lymphocytes drives the recruitment to rafts and the interaction of both CD26 and CD45RO [112], which probably causes CD45 dimer dissociation [112], increased PTPase activity [124] and a signal transduction cascade that both overlaps with and boost the TCR pathway [112, 125–128] (Fig. 1).

This potentially detrimental function of CD26 to the lungs of a person with asthma seems to involve the active centre [112, 129], but not necessarily the DPP4 activity. Thus, CD26 on T_H cells recognizes caveolin-1 and induces the upregulation of the proinflammatory B7.2/CD86 molecule in APCs [113, 129]. In T cells, CD26-caveolin-1 interaction induces the coalescence of lipid rafts, recruitment of CARMA1 and activation/nuclear translocation of the proinflammatory and "rapid acting" transcription factor NF-kB [130] (Fig. 1). Therefore, the CD26$^{+/high}$ phenotype of Teff cells may favour allergen-induced inflammation in lungs [131], while the CD26$^{-/low}$ phenotype of Treg cells may contribute to keep low levels of CD86 on APCs and trigger anergy/apoptosis in allergen-specific naïve T cells. However, all these findings about the costimulatory role of CD26 need further clarification, as either a partial or complete genetic deletion of CD26 or the use of CD26 inhibitors does not impact this function [132, 133].

The costimulatory actions of CD26 also could depend on the interaction with another enzyme: ADA [111, 134–136]. Most of ADA molecules in lymphocytes are cytosolic, but a small proportion (10 %) are associated with either CD26 [111, 134, 135] or Ado receptors (ARs: A_1AR and A_{2B}AR) on the T cell membrane (ecto-ADA) [114, 135–138]. Binding of ADA to CD26 takes place in human (but not murine) lymphocytes [25, 63], and this interaction could potentially trigger a costimulatory signal that favours lymphocyte proliferation and T_{H1} cytokine and chemokine production [139–141] (Fig. 1). In turn, activation through the TCR/CD3 complex and costimulation with T_{H1} (but not T_{H2}) cytokines increase the number of ecto-ADA molecules [63, 139] and the formation of the ADA-CXCR4-CD26 triad [114], which might help to trap the chemokine receptor CXCR4 at the immunological synapse to make lymphocytes insensitive to the chemokine stromal cell-derived factor α (SDF1α/CXCL12) and trigger a proliferative and cytokine-secreting response [142] (Fig. 1).

Costimulatory effects could also come from sCD26, which is capable of enhancing the T cell-mediated reaction against recall antigens (e.g., tetanus toxoid) or suboptimal amounts of polyclonal stimuli (PHA or anti-CD3) [143, 144]. Contrary to initial results [143], the most recent data point out that this proinflammatory effect of sCD26 is not dependent on CD26 or ADA-binding activities [145] and is likely triggered upon interaction with proteins like caveolin-1 [113, 129, 130] or insulin-like growth factor II/mannose-6-phosphate (IGF-II/M6P) receptor [146, 147] in APCs or protease-activated receptor 2 (PAR2) in smooth muscle cells [148]. sCD26 promotes CD86 upregulation in APCs [113, 129, 146] and the generation of reactive oxygen species (ROS) and toll-like receptors [149] (Fig. 1).

CD26 is the major member of the prolyl oligopeptidase family and cleaves X-proline or X-alanine dipeptides from the *N*-terminus of different polypeptides, even though other

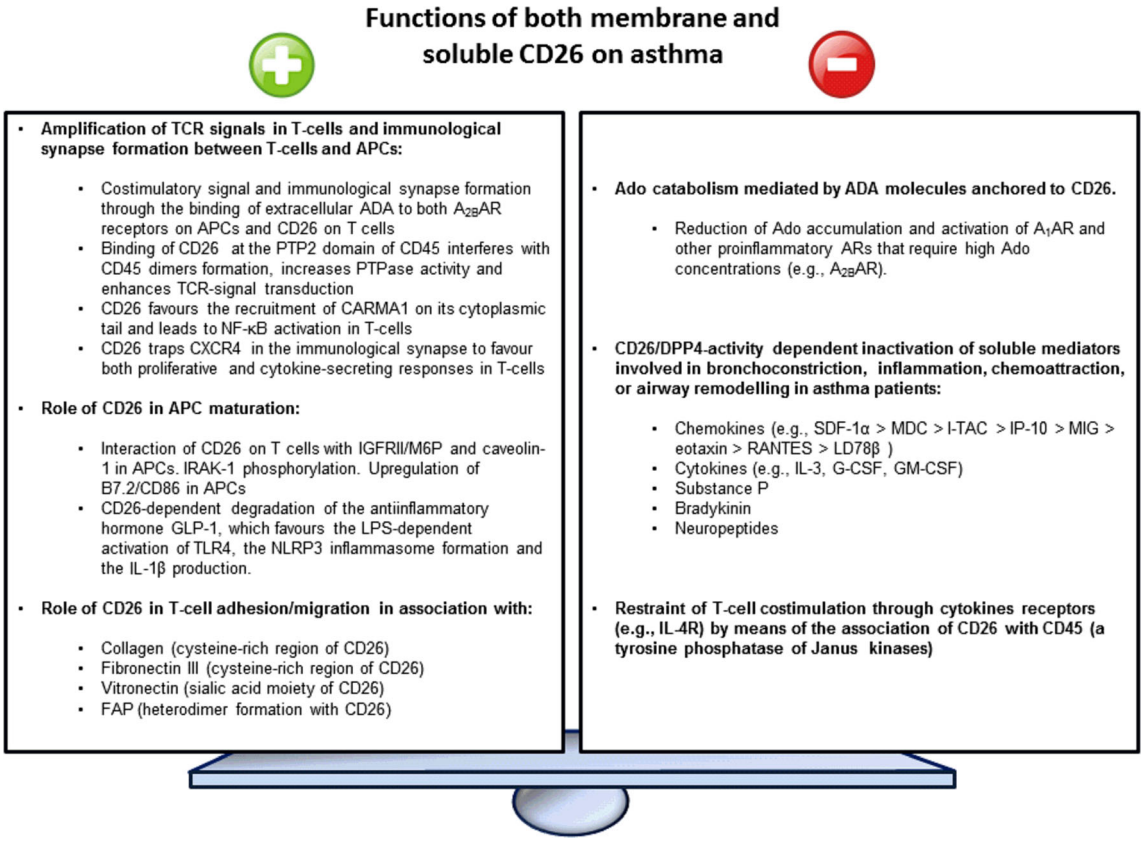

Fig. 1 Functions of both membrane and soluble CD26 on asthma. This figure summarizes both positive (i.e., those that favour asthma development or exacerbation) and negative (i.e., those that prevent asthma development or exacerbation) functions of CD26 on this disease

amino acids are accepted with lower efficiency: Pro > Ala > Hyp>> Ser > Gly > Val > Leu [25]. Apart from the primary sequence, the 3D structure, size and substrate ionization (optimum pH 7.5–8.5) significantly influence the catalytic efficiency of CD26 [10, 94, 100, 150, 151]. Peptides containing X-proline or X-alanine at the *N*-terminus are not easy to process by most of proteases [152], which means that CD26 has a key biological role. Indeed, DPP4 activity has been linked to the activation of T lymphocytes in response to extracellular stimuli. For example, Jurkat cells transfected with CD26 display greater activation than those expressing DPP4-deficient CD26 molecules [153]. DPP4 activity is also necessary in sCD26 molecules to boost the tetanus toxoid-dependent proliferation [146]. CD26 inhibitors yield similar results in vitro, with suppression of T cell proliferation and secretion of proinflammatory cytokines but enhanced release of TGF-β1 [154–157]. In vivo, the use of CD26 inhibitors in murine models of human diseases like rheumatoid arthritis [158], multiple sclerosis [159] or asthma (aerosolized simultaneously with the allergen) [45] also describes a proinflammatory role of CD26. Moreover, CD26 inhibitors also support a positive role of CD26 in NLRP3 inflammasome formation [160]. However, enzyme activity is required, but not in absolute terms, during the costimulatory function of CD26, since this biological activity is retained after deleting part of the hydrolase domain [132] (Fig. 1).

Inhibitory Functions of Both Membrane and Soluble CD26 on Asthma

Apart from its costimulatory and asthma-detrimental role, there is also evidence that CD26 exhibits other asthma-preventive activities. This protective function of CD26 is linked to the indirect or direct control of different soluble mediators like Ado, bradykinin or neuropeptides that are involved in bronchoconstriction, inflammation, chemoattraction or airway remodelling in asthma patients [161]. For instance, the nucleoside Ado is the substrate of ADA, an enzyme that catalyses its irreversible deamination to inosine [139, 140]. As already mentioned, ADA has been found anchored to CD26 (Fig. 1) in many cells, but two frequently regarded proinflammatory ARs (A_1AR and A_{2B}AR) also interact with this enzyme, which seems important for their efficient ligand-dependent signalling [111, 134–138]. ARs are novel targets for treatment of human asthma, and some antagonists and agonists have entered the clinical phase with a not totally clear efficacy [161, 162]. Indeed, there is an elevated expression of asthma-favouring and ADA-interacting receptors A_1AR and A_{2B}AR in bronchial tissue [161, 162], but probably reduced amounts of asthma-protective A_{2A}AR [161]. In addition, there is an augmented Ado concentration in the extracellular compartment in asthma. This nucleoside plays a detrimental role in

this disease by causing bronchoconstriction, airway inflammation (e.g., mast cell degranulation, airway accumulation of eosinophils), airway remodelling, edema or mucus production [161, 162]. These harmful effects also depend on the specific engaged type I purinergic receptor and the particular cells expressing the ARs in airways (e.g., APCs, lymphocytes, eosinophils, neutrophils, endothelial and mast, epithelial, endothelial and smooth muscle cells) [161, 162]. This role of Ado in asthma is affected by binding affinity, receptor density and local levels of this nucleoside, which are influenced by a delicate balance where different mechanisms are involved (e.g., extracellular/intracellular Ado metabolism) [161, 162]. Amongst these mechanisms, the Ado catabolism mediated by ADA molecules anchored to CD26 is the major regulated pathway that influences the local concentration and biological effects of Ado. In this respect, relevant T_{H2} cytokines in allergic asthma (IL-4, IL-13) reduce ADA activity in the lung [161] and ecto-ADA levels on T_H lymphocytes [63]. These findings suggest that low levels of CD26/ecto-ADA on the T_{H2} subset in T_{H2}^{high} (allergic/atopic) asthma could favour the local accumulation of Ado, the activation of A_1AR and the participation of proinflammatory ARs that require Ado concentrations over the physiological levels (e.g., the low-affinity $A_{2B}AR$) in order to neutralize the off-signals provided by the engagement of high-affinity and asthma-protective $A_{2A}ARs$. Therefore, it is likely that AR-targeted therapy is more effective in T_{H2}^{high} asthma than in T_{H2}^{low} or severe asthma, wherein CD26/ecto-ADA^{high} T_{H1} and T_{H17} cells are more frequent. Moreover, additional studies are needed to clarify what could be exactly the role of Treg cells in asthma, a lymphocyte subset with a CD26/ecto-ADA^{low} phenotype that should favour the high production of Ado [70]. On the other hand, CD45 has been involved in Janus kinase dephosphorylation [163]. Therefore, the CD26-CD45 association could have a negative and DPP4-independent role important to restrain the signal transduction of cytokine receptors [122] (Fig. 1). In this sense, the low PTPase activity in human naïve $CD4^+CD45RA^+CD26^{-/low}$ T cells makes them susceptible to small amounts of IL-4, as mentioned as an important cytokine in allergic asthma, while memory/effector $CD4^+CD45RO^+CD26^{+/high}$ T cells secrete this soluble factor upon activation, but are less sensitive to its effects [164]. Indeed, high levels of CD26 in memory/effector T_H lymphocytes might act as a "brake" for the proliferative responses to cytokines (for example, IL-12; our unpublished results).

The protective function of CD26 in asthma could also be linked to the DPP4 activity (Fig. 1). Some CD26 substrates fall outside the scope of the immune system and this review, like incretins (glucose-dependent insulinotropic peptide (GIP), glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2)) [10, 165, 166], glucagon, pituitary adenylate cyclase-activating polypeptide (PACAP), gastrin-releasing peptide (GRP), peptide YY, vasoactive peptides (bradykinin and vasoactive intestinal peptide (VIP)), natriuretic peptides (B-type natriuretic peptide (BNP)) and neuropeptides (neuropeptide Y (NPY), beta-casomorphins, endomorphins, substance P) [41, 82, 166, 167] (Table 2). However, some others have an important immunomodulatory role, such as cytokines (e.g., IL-3, G-CSF, GM-CSF) [168] or chemokines (e.g., RANTES/CCL5, eotaxin/CCL11, MDC/CCL22) [82, 166]. CD26 enzymatic activity downmodulates the biological function of most of these chemokines and cytokines (Table 3). Consistent with this observation, it has been found that CD26 inhibitors can enhance some in vivo immune responses depending on the dose, application route, timing or predominant Teff subset [45, 169], which could be explained by the presence of off-target effects as well [25, 170]. However, animal models of rheumatoid arthritis [93], multiple sclerosis [171] and inflammatory bowel disease [172] in CD26 KO mice do support an immunosuppressive role of both CD26 and DPP4 activity. This immunosuppressive function has also been observed for sCD26 during strong in vitro proliferative responses of immune cells [143, 145]. Moreover, CD26 has been even regarded a tumour suppressor gene in melanomas or neuroblastomas [173, 174]. For this reason, we will focus this part of this review on the CD26 substrates with a direct connection with the immune system like chemokines.

CD26, T_{H2}-Related Chemokines and T_{H2}^{high} Asthma

Even though cytokines like IL-1β or IL-2 contain an appropriate *N*-terminal sequence, the molecular weight precludes their *N*-terminal clipping, with exceptions like IL-3, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) or erythropoietin (Epo) [168]. In contrast, CD26-dependent processing of chemokines (8–10 kDa) like RANTES (regulated on activation, normal T cell expressed and secreted) is one of the most interesting aspects of CD26 biology [175]. Moreover, this function is mostly dependent on CD26 levels, which is influenced by the T cell subset or disease, as we have just seen.

Chemokines are proinflammatory cytokines with a role in leukocyte activation and migration. They are classified according to the position of two *N*-terminal cysteine residues (CC, CXC, C and CX3C) [176] but can also be divided as a function of the cells they attract or the receptor they recognize. As Table 3 shows, the major branches of effector (T_{H1}, T_{H2} and T_{H17}) and regulatory T cells express characteristic (but not totally selective) chemokine receptors [76, 103]. For example, T_{H2} lymphocytes and other leukocytes important in asthma (basophils, mast cells and eosinophils) express CCR3, CCR4, CCR8, CXCR4 and, in humans, CRTH2 [103]. CCR3, CCR4 and CXCR4 interact with CD26 substrates, but only CCR3 and CCR4 are actually specific for T_{H2} cells. Regarding CXCR4,

Table 2 Known substrates processed by CD26/DPP4 out of the immune system

Substrate name and family	*N*-terminal sequence	Effect of DPP4 processing	In vitro/in vivo evidence	Reference
β-Casomorphins (neuropeptide)	Tyr-Pro▼Phe	Inhibitory	Yes/yes	[10, 82, 167]
BNP (natriuretic peptide)	Ser-Pro▼Lys	Inhibitory Change in receptor preference	Yes/yes	[82, 248]
Bradykinin (vasoactive)	Arg-Pro▼Pro	Inhibitory Change in receptor preference	Yes/yes	[10, 82, 167]
Endomorphins (neuropeptide)	Tyr-Pro▼Phe	Inhibitory Change in receptor preference	Yes/yes	[10, 41, 82, 167]
Enterostatin (gastrointestinal hormone)	Val-Pro▼Asp	Inhibitory	Yes/yes	[10, 41, 167]
GIP (incretin)	Tyr-Ala▼Glu	Inhibitory	Yes/yes	[10, 41, 82, 165, 167]
GLP: GLP-1 (7-36) amide, GLP-1 (7-37)[b] and GLP-2 (incretin)	His-Ala▼Glu (GLP-1) His-Ala▼Asp (GLP-2)	Inhibitory	Yes/yes	[10, 41, 82, 165, 167]
Glucagon (gastrointestinal hormone)[a]	His-Ser▼Gln	Inhibitory	Yes/yes	[82, 167]
GRH: GRH (1-29) and GRH (1-44) (hypothalamic hormone)	Tyr-Ala▼Asp	Inhibitory	Yes/no	[10]
GRP (bombesin family hormone)	Val-Pro▼Leu	Not known	Yes/yes	[82]
NPY (neuropeptide)	Tyr-Pro▼Ser	Receptor Y1 Inactivation Change in receptor preference	Yes/yes	[10, 41, 82, 167]
PACAP (PACAP27 and PACAP38)[a]	His-Ser▼Asp	Probably inhibitory	Yes/yes	[82, 249]
Peptide YY (pancreatic peptide)	Tyr-Pro▼Ile	Receptor Y1 Inactivation Change in receptor preference	Yes/yes	[10, 41, 82, 167]
Substance P (neuropeptide)	Arg-Pro▼Lys	Inhibitory Questionable	Yes/yes	[10, 41, 82, 167]
VIP peptides (VIP, PHV42, PHM27) (vasoactive)[a]	His-Ala▼Asp (PHV, PHM) His-Ser▼Asp (VIP)	Probably inhibitory	Yes/yes	[10, 41, 82, 165, 167]

BNP B-type natriuretic peptide, *GIP* glucagon inhibitory peptide, *GLP* glucagon-like peptide, *GRH* growth hormone-releasing hormone, *GRP* gastrin-releasing peptide, *NPY* neuropeptide Y, *PCAP* pituitary adenylate cyclase-activating polypeptide, *VIP* vasoactive intestinal peptide, *PHV42* peptide histidin valin 42, *PHM27* peptide histidin methionine 27

[a] Glucagon, PACAP and VIP have a Ser in position 2 and, with less efficiency than Pro or Ala, also can be a DPP4 potential substrate

[b] GLP-1 (7-36) amide and (7-37) are the active forms of GLP-1 and substrates of DPP4

T_{H2} cells seem to display a slight overexpression compared to T_{H1} lymphocytes [177], but other authors describe CXCR4 as a merely trafficking marker [178–180].

Ligation of CCR3 with eotaxin/CCL11; RANTES/CCL5; and MCP-1/CCL2, MCP-2/CCL8, MCP-3/CCL7 and MCP-4/CCL13 participates in the recruitment of basophils, eosinophils and mast cells [103, 181, 182] (Table 3). Eotaxin is an important chemokine in allergic asthma produced by endothelial cells and monocytes in response to IFNγ and TNFα, respectively. This chemokine is recognized by CCR3 (eosinophils, basophils, mast cells and T_{H2}) and at lesser extent by CCR5, a putative T_{H1} marker (see later) [183]. Eotaxin is a chemoattractant for eosinophils that facilitates their mobilization from bone marrow [184]. Truncation of eotaxin by CD26 is characterized by an intermediate-low efficiency (k_{cat}/K_m: SDF1α > MDC > I-TAC > IP-10 > MIG > eotaxin > RANTES > LD78β) [185]. Despite this, *N*-terminal clipping by CD26 results in an isoform (3–74) with reduced chemotactic activity that causes CCR3 desensitization [183, 186, 187]. Indeed, administration of eotaxin to F344 rats leads to a mobilization of eosinophils, an effect enhanced in CD26-deficient animals or with CD26 inhibitors [187]. Additionally, $CD26^{-/-}$ mice challenged with ovalbumin (OVA) show higher levels of CCR3 and CCR3 ligands (eotaxin, RANTES) and stronger eosinophil infiltration in lungs [16]. Another ligand of CCR3 is CCL14 (Table 3), a chemokine processed by plasmin and urokinase plasminogen activator (UPA) to yield CCL14 (9–74). This isoform binds to CCR3 (and also CCR1 and CCR5) to efficiently attract eosinophils, monocytes and T_{H2} cells, a process also dampened by CD26 [188]. Therefore, a $CD26^{-/low}$ phenotype in both eosinophils and T_{H2} cells ($CCR3^{+}$) seems to favour the inflammatory response in T_{H2}^{high} asthma.

CXCR4 is found in monocytes and B/T (preferentially T_{H2}) cells [177, 189] and promotes the recruitment of T cells in lungs during allergic airway diseases [178, 190]. CXCR4 recognizes macrophage migration inhibitory factor (MIF) and stromal cell-derived factor 1 (SDF1/CXCL12) [189] (Table 3), the last one a small chemokine synthesized by endothelial cells and fibroblasts that induces T/B cell activation [142] and regulates the traffic of lymphocytes, monocytes and dendritic cells

Table 3 Chemokines processed by CD26/DPP4

T_H subset	Chemokine receptor expressed:	Common ligands of these receptors	Substrates of DPP4 activity	Effect of clipping on chemokine activity or receptor preference	*N*-terminal cleavage	M_r (Da) expasy	Half-life (min)	K_{CAT}/K_M ($10^{-6}M^{-1}S^{-1}$)	References
Treg (FoxP3, CD26$^{-/low}$)	CCR4	CCL17/TARC (n.d.)	No						
		CCL22/MDC	Yes	↓, RP	Gly-Pro▼Tyr	8090.47	1.6	4 ± 1	[10, 41, 82, 166, 167, 185]
	CCR6	CCL20/MIP-3α (n.d.)	No						
T_{H2} (GATA3, CRTH2, CD30, CD26^{+})	CCR3	CCL5/RANTES	Yes	RP	Ser-Pro▼Tyr	7851.01	400	0.04 ± 0.01	[10, 41, 82, 167, 185]
		CCL11/eotaxin 1	Yes	↓	Gly-Pro▼Ala	8364.90	30	0.08 ± 0.01	[10, 41, 82, 166, 167, 185]
		CCL24/eotaxin 2 (n.d.)	No						
		CCL26/eotaxin 3 (n.d.)	No						
		CCL8/MCP2 (n.d.)	No						
		CCL7/MCP3 (n.d.)	No						
		CCL13/MCP4	No						
		CCL14a [9–74]	Yes	↓	Gly-Pro▼Tyr	7800.83	n.d.	n.d.	[188]
		CCL15/MIP-5	No						
		CCL28/MEC	No						
	CCR4	CCL17/TARC	No						
		CCL22/MDC	Yes	↓, RP	Gly-Pro▼Tyr	8090.47	1.6	4 ± 1	[10, 41, 82, 166, 167, 185]
	CCR8	CCL1	No						
		CCL17/TARC	No						
	CXCR4	CXCL12/SDF-1α	Yes	↓, CXCR4 antagonist	Lys-Pro▼Val	7609.97	<1	5 ± 2	[10, 41, 82, 166, 167, 185]
T_{H1} (t-bet, CD26^{++})	CCR5	CCL3L1/LD78β	Yes	↑, RP	Ala-Pro▼Lys	7797.74	6000	0.003 ± 0.002	[82, 166, 167, 185]
		CCL4/MIP-1β	No						
		CCL5/RANTES	Yes	RP	Ser-Pro▼Tyr	7851.01	400	0.04 ± 0.01	[10, 41, 82, 167, 185]
		CCL8/MCP2	No						
		CCL7/MCP3	No						
		CCL13/MCP4	No						
		CCL11/Eotaxin	Yes	↓	Gly-Pro▼Ala	8364.90	30	0.08 ± 0.01	[10, 41, 82, 166, 167, 185]
		CCL14a/HCC-1[9–74]	Yes	↓	Gly-Pro▼Tyr	7800.83	n.d.	n.d.	[188]
		CCL16	No						
		CCL23/MPIF-1	No						
	CXCR3A	CXCL9/Mig	Yes	↓, CXCR3 antagonist	Thr-Pro▼Val	11724.81	24	>0.4 ± 0.2	[82, 166, 167, 185]
		CXCL10/IP-10	Yes	↓, CXCR3 antagonist	Val-Pro▼Leu	8646.30	4	0.5 ± 1	[10, 41, 82, 166, 167, 185]
		CXCL11/I-TAC	Yes	↓, CXCR3 antagonist	Phe-Pro▼Met	8307.01	2	1.2 ± 0.1	[82, 166, 167, 185]

Table 3 (continued)

T_H subset	Chemokine receptor expressed:	Common ligands of these receptors	Substrates of DPP4 activity	Effect of clipping on chemokine activity or receptor preference	*N*-terminal cleavage	M_r (Da) expasy	Half-life (min)	K_{CAT}/K_M ($10^{-6}M^{-1}S^{-1}$)	References
T_{H17} (RORγT, CD26^{+++})	CCR4	CCL17/TARC	No						
		CCL22/MDC	Yes	↓, RP	Gly-Pro▼Tyr	8090.47	1.6	4 ± 1	[10, 41, 82, 166, 167, 185]
	CCR6	CCL20/MIP-3α	No						

CCR C–C motif chemokine receptor, *CXCR* C–X–C motif chemokine receptor, *CCL* C–C motif chemokine ligand, *CXCL* C–X–C motif chemokine ligand, *TARC* thymus and activation-regulated chemokine, *MDC* macrophage-derived chemokine, *MIP-3α* macrophage inflammatory protein-3 α, *RANTES* regulated on activation, normal T cell expressed and secreted, *MCP(2, 3 and 4)* monocyte chemotactic protein, *MIP5* macrophage inflammatory protein 5, *MEC* mucosae-associated epithelial chemokine, *SDF-1α* stromal cell-derived factor 1 α, *MIP-1β* macrophage inflammatory protein-1β, *MPIF-1* myeloid progenitor inhibitory factor 1, *Mig* monokine induced by γ-interferon, *IP-10* 10-kDa interferon γ-induced protein, *I-TAC* interferon-inducible T-cell α chemoattractant, *RP* change in receptor preference, ↓↑ change in activity/function, *n.d* not determined

towards inflamed epithelia [179, 189, 191, 192]. Amongst the several SDF1 isoforms, at least two (SDF1α and SDF1β) are efficiently processed by CD26 in vitro [185, 193–195] and in vivo [93]. The SDF1α (3–67) isoform is unable to activate CXCR4 and displays antagonistic activity [185, 193–198]. Moreover, both CD26 and CXCR4 have similar expression kinetics upon activation [58, 199] and interact in lymphocytes [114]. Binding of SDF1α to CXCR4 initiates the CXCR4-CD26 complex endocytosis [114], a process disrupted by *N*-terminal clipping of SDF1α [195]. This finding could not explain however the preferential expression of CXCR4 in CD26^{low} cells (e.g., T_{H2} or naïve T_H) [76, 199] or why TGF-β (a cytokine that induces CD26 downmodulation) leads to augmented expression of CXCR4 and a potentiated SDF1α-CXCR4 axis [200–202]. This CD26$^{-/low}$CXCR4^{+} phenotype also facilitates a vigorous response to SDF1α in the recruitment of T cells and eosinophils in a mouse model of lung allergic inflammation [178]. On the other hand, CD26 has also been positively correlated with the in vitro invasive capacity of T cell lines in response to SDF1α, and this positive effect is mediated by CD45 [203], a tyrosine phosphatase that enhances cell migration in response to SDF1α [204].

CCR4 is present on monocytes, dendritic cells, NK cells and T_H cells (T_{H2}, T_{H17}, Treg). CCR4 recognizes both CCL17/TARC and CCL22/MDC (Table 3), the last chemokine produced by macrophages, dendritic cells, NK cells and B/T lymphocytes [205]. TARC and MDC are expressed by epithelial cells in the airways, and their levels are upregulated after allergen challenge [103]. T_{H2} cytokines (e.g., IL-4 and IL-13), LPS, IL-1 and TNFα stimulate the secretion of MDC, whereas T_{H1} cytokines (e.g., IFNα, IL-12) inhibit MDC production [205, 206]. Moreover, MDC generates and amplifies T_{H2} responses and recruits T_{H2} lymphocytes [205–207], being important in diseases with a T_{H2}-cytokine profile (e.g., asthma) or equivalent models in mice [207]. In these models, CCR4-MDC has a dominant role in later and chronic stages of the disease as compared with CCR3-eotaxin [181]. Furthermore, CD26 processes MDC (half-life 2–5 min) very efficiently to generate MDC(3–69) and, subsequently, MDC(5–69) [185]. This last isoform preserves the attractant power for monocytes, but displays reduced chemotactic activity for lymphocytes and dendritic cells [150], two subsets important in asthma. As Tregs, T_{H2} and CCR4^{+} T_{H17} cells are CD26$^{-/low}$ cells, while CCR4^{-} T_{H17} cells are CD26^{high} cells [72, 79], the CD26$^{-/low}$ phenotype of these CCR4^{+} subsets should apparently facilitate their recruitment to inflammatory sites.

CD26, T_{H1}/T_{H17}-Related Chemokines and T_{H2}^{low} Asthma

Most of asthma patients present a T_{H2}^{high} disease, but there are other two types (obesity-associated and neutrophilic asthma) linked to a T_{H2}^{low} (i.e., T_{H1}/T_{H17}) profile [1]. The CD26^{high} T cell subset displays a CD45RO^{+}CCR7^{low} effector-memory phenotype and produces T_{H1}/T_{H17} cytokines [72, 77, 208]. T_{H1} cells are CCR5^{+}CXCR3A^{+} lymphocytes [72, 208]; are essential for the production of IgM, IgG and IgA (but not IgE) by B cells; and orchestrate the response against intracellular microbes [103]. A few CCR5 ligands and all the CXCR3A-specific chemokines are CD26 substrates (Table 3). For example, CCL5/RANTES is produced by endothelial and epithelial cells, platelets, macrophages, eosinophils and T cells [209]. RANTES activates CCR1, CCR3 (T_{H2}) and preferentially CCR5 (T_{H1}), thereby attracting monocytes, eosinophils and T cells to inflammatory sites [209]. This chemokine is cleaved with a low efficiency (half-life of 400 min) by CD26 [100, 185], leading to RANTES(3–68), a chemokine that loses its capacity to bind CCR1 and CCR3 (monocytes, eosinophils and T_{H2} cells), but not CCR5 [197]. As CCR5 is expressed on T_{H1} and CD45RA^{-}CD45R0^{+}CCR7^{low} effector-memory

$CD4^+$ T cells (both $CD26^{+/high}$) [76, 103, 199], this means that RANTES(3–68) favours their attraction towards inflammatory sites [175, 197, 198, 210].

Another T_{H1} chemokine and CD26 substrate that binds CCR5 is LD78β/CCL3L1 [211]. Macrophage inflammatory protein-1α (MIP-1α) is encoded by two different loci: LD78α and LD78β [212]. Both chemokines are agonists of CCR1, CCR3 and CCR5, but LD78β binds with high affinity to CCR5 [213], regulating the traffic/activation of macrophages/monocytes, NK cells, eosinophils, basophils, immature dendritic cells and T lymphocytes. Strikingly, the inefficient (half-life ~ 5 h) [185, 211] clipping of LD78β by CD26 generates LD78β(3–70) and enhances the chemotactic activity for T_{H1} cells (CCR5) and monocytes/neutrophils (CCR1) (Table 3). This fact, together with the $CCR1^{low}$ phenotype in eosinophils (<20 %) and the reduced affinity of LD78β (3–70) for CCR3 (T_{H2}), proves once again that this posttranslational modification tends to favour T_{H1} responses [211, 214].

CXCR3A is overrepresented on T_{H1} cells [208] and is recognized by IFNγ-induced chemokines (CXCL9/Mig, CXCL10/IP-10, CXCL11/I-TAC) secreted by endothelial cells, hepatocytes, fibroblasts, keratinocytes and leucocytes in response to infections and several diseases including asthma. These chemokines are important to bring T_{H1} cells into epithelial barriers [103]. Moreover, after being *N*-terminally processed by CD26 with intermediate-high efficiency [185] (Table 3), they become less active T_{H1} chemoattractants. In addition, this modification also makes IP-10 a CXCR3 antagonist and induces receptor desensitization, being part of a negative feedback mechanism important to downmodulate inflammation [215–217].

T_{H17} lymphocytes play a major role in tissue inflammation, are essential to activate macrophages and recruit neutrophils and drive the defensive activities against extracellular bacteria and fungi. Human T_{H17} cells are associated with the expression of CCR4, CCR6 and CXCR6 [72, 103, 218]. Skin-homing addressins (e.g., CCR4, CCR6) are also shared by $CD26^{-/low}$ Treg cells and T_{H2} cells [73]. However, T_{H17} cells are rare at sites of inflammation, maybe due to homeostatic mechanisms that avoid their expansion, a high plasticity to shift to T_{H1} cells [103] or the heterogeneous expression of CCR4, with a proinflammatory $CCR4^-CCR6^+CD26^{high}$ phenotype in most of T_{H17} cells and a small subset of immunosuppressive $CCR4^+CCR6^+CD26^{low}$ [79, 81]. This heterogeneity for CCR4 is also detected in T_{H22} cells, a lineage that produces IL-22; expresses CLA, CCR6 and CCR10; and plays an anti-inflammatory and tissue-protective role in asthma [219]. Curiously, $CCR4^-$ T_{H22} cells are $CD26^-$, whereas $CCR4^+$ T_{H22} cells are constituted by either $CD26^-$ or $CD26^+$ lymphocytes [79].

In summary, taking into consideration the CD26 expression gradient in the major T_H subsets ($T_{H17} >> T_{H1} > T_{H2} >> T_{reg}$), the small proportion of chemokines affecting $T_{reg}/T_{H2}/T_{H17}$ cells that are processed by CD26 as compared with those recruiting T_{H1} cells and that CD26-dependent clipping produces a drop in the biological functions of most of them, it is evident that CD26 forms part of a homeostatic mechanism to downmodulate airway inflammation mediated by T_{H2} and especially T_{H17}/T_{H1} cells (e.g., obesity-linked asthma).

CD26 and Asthma: Animal Models, Studies in Human System and Clinical Implications

Despite the reported evidences on a role of CD26 in T_{H1}-related diseases, the involvement of both the peptidase-dependent and peptidase-independent functions of CD26 in the pathophysiology of asthma is not yet fully understood. In this section, we summarize some results obtained in animal models and the human system.

Rat Models

Rat models using inhaled allergens such as OVA have been used to evaluate the role of CD26 in bronchial asthma. Thus, the severity of the airway inflammation decreases as the endogenous CD26 level of the strain becomes lower [220], likely due to the costimulatory role of CD26. One of the models more extensively used is the F344 strain. Challenge of F344 rats with OVA generates bronchoconstriction and higher CD26 expression on lymphocytes and epithelial cells of lung parenchyma [14, 17]; enhanced levels of DPP8/9 and DPP10 in bronchi [17]; and a dose-dependent recruitment to the lungs of dendritic cells, eosinophils and $CD4^+CD25^+CD26^+$ T cells [14]. More specifically, OVA causes increased recruitment of T cells to bronchi (but not lung parenchyma) [22] and enhanced sDPP4 activity in bronchoalveolar lavage fluid (BALF) [17], the last finding likely related with the augmented presence of $CD26^-$ T cells in bronchi. Interestingly, there is a F344 substrain with an active-site mutation in the *Dpp4* gene that causes protein retention/degradation in the endoplasmic reticulum and lower CD26 levels [221]. This F344 substrain also displays the early bronchoconstriction in response to OVA challenge [222], but the late inflammatory response is milder regarding OVA-specific serum IgE, eosinophilia and recruitment of T cells in both bronchi and BALF [14, 22, 220]. In contrast, entrance of T cells in bronchoalveolar lymphoid tissue (BALT) is enhanced, no matter the $CD26^+$ or $CD26^-$ phenotype of transferred T cells [223].

Because bronchi are $DPP4^-$ (but $DPP8/9/10^+$) compartments [17], $CD4^+CD25^+$ T cells recruited in the airways of OVA-challenged F344 rats are either T_H cells with a $CD26^{low}$ phenotype or they downmodulate CD26 during peribronchial

infiltration. Thus, a potential higher response of $CD4^+CD25^+CD26^+$ T cells to SDF1α [203] could allow their recruitment to bronchi ($CD26^-$ SDF-1^{high} environment) of wild-type rats [22] with a concomitant SDF1-driven downmodulation of CD26, as it happens during skin homing of Sézari cells [224]. In contrast, $CD4^+CD25^+CD26^-$ Teff cells in CD26-deficient rats would not be attracted to the bronchi as a result from either an anomalous/aberrant response to SDF1α [203] or a reduced chemokine gradient [22], resulting in a milder asthma-like disease. However, despite that SDF1 is augmented in the bronchi of asthmatic patients [225], OVA challenge does not increase the number of SDF1 transcripts in the large airways of F344 rats [22]. Curiously, the amount of SDF1 is increased in the BALT of CD26-deficient rats, likely supporting the above commented higher recruitment of T cells to this lymphoid compartment after OVA challenge [223].

CD26-deficient F344 rats display a parallel increased influx of Tregs into the lungs, with a concomitant raise in the IL-10 production that explains the diminished inflammation [222]. However, this may not happen in the same way in humans, where Treg cells display a $CD26^{-/low}$ phenotype [69–72] in contrast to rats [14, 68]. Moreover, it is difficult to conciliate a milder asthmatic-like inflammation in OVA-challenged CD26-deficient F344 rats with either a lower truncation rate of T_{H2} chemokines (e.g., eotaxin) or the in vivo enhanced eotaxin-mediated recruitment of eosinophils caused by a CD26 inhibitor [187]. Perhaps the different genetic background [226] or the administration route might play a significant role [45]. For example, oral administrated inhibitors seem to enhance allergic inflammation of the airways, whereas topic inhibition (aerosolization) has a rather protective effect in line with that observed in CD26-deficient F344 rats [45]. Moreover, dual deficiency of enzymatic and extraenzymatic activities of CD26 in murine asthma models may generate results different from the observed effects of CD26 inhibitors, which only inhibit enzymatic functions [166].

Mouse Models

CD26 KO mice display a healthy phenotype, with increased glucose clearance, resistance to obesity and small changes in the percentages of NK, NKT and $CD4^+$ T cells [227, 228]. In addition, in vitro pokeweed mitogen (PWM)-activated splenocytes from $CD26^{-/-}$ C56BL/6 mice show a decreased IL-4 production, while IgE and IL-4 are significantly reduced in sera from $CD26^{-/-}$ animals upon PWM treatment [228]. In clear contrast, Yan et al. reported in 2012 unchanged IgE concentration but enhanced eosinophilia and T_{H2} cytokines (IL-4, IL-5, IL-13) in BALF from OVA-induced $CD26^{-/-}$ C56BL/6 animals, as well as higher mRNA and protein levels of CD26 substrates (eotaxin and RANTES) and chemokine receptors (CCR3 and CCR5) [16]. These partially contradictory results probably depend on the type, administration route and strength of the polyclonal stimulus (PWM vs. OVA) [16]. They also point out that induced and targeted (cell type-specific) KO models could be necessary to truly dissect the role of CD26 in asthma [16].

Human System

In line with the small differences in CD26 levels observed between T_{H1} and T_{H2} cells [72], this marker is not helpful to differentiate T_{H1}- from T_{H2}-driven responses in patients with atopic asthma [229]. However, augmented CD26 levels are actually detected on total lymphocytes, $CD4^+$ T cells and iNKT (but not $CD8^+$ T lymphocytes, monocytes or B cells) in adult allergic asthma, reflecting the existence of an activated status [20]. This last work also published an elevation of plasma sCD26 in patients, which was associated with eosinophil counts and IgE concentration. Additionally, this group reported a lower production of T_{H1} chemokines (IP-10, MIG) and higher presence of other chemokines (RANTES, MDC) and their receptors (CCR3, CCR4), in both cases attributable to a T_{H2}-response predominance [20]. In clear contrast, Matsuno et al. found that sCD26 is inversely correlated with the inflammation level in chronic eosinophilic pneumonia, a disease frequently preceded or accompanied by asthma [230]. More recently, no differences were found in serum sCD26 levels in children with asthma or association of this variable with either asthma or atopy (e.g., skin prick test, IgE, eosinophil cationic protein) [86].

From the analysis of all these studies, the need to expand them to different asthmatic phenotypes (or endotypes) and levels of severity/chronicity is obvious. In addition, it is also clear that other variables (sample size, lymphocytes counts, age, sex) should also be taken into account, especially knowing (a) the influence of sex on membrane-bound CD26 (our unpublished results) and sCD26 levels [86–89, 91] and (b) the augmented prevalence of asthma in boys at early ages and the higher prevalence of asthma in women after puberty [5, 6], especially in the case of certain T_{H2}^{low} phenotypes [1]. For example, sCD26 is apparently increased in the blood of both atopic dermatitis (a T_{H2}-like disease) [231] and adult asthma patients [20], but in the last study these results might be partially explained by a higher proportion of males in the group of patients. In contrast, Remes did not show altered sCD26 levels in asthmatic children and took into consideration certain pre-analytical variables (gender, age) [86]. Therefore, more studies are needed to reveal the potential correlation between CD26/sCD26 and the severity and phenotype of the asthmatic pathology.

Clinical Implications

High body mass index is a factor with a positive association with asthma development and severity [3, 232, 233]. This

association of asthma and obesity appears to be stronger in women than in men, with a role for both non-inflammatory and subclinical/systemic chronic inflammatory pathways, including the release of proinflammatory (e.g., leptin) or anti-inflammatory (e.g., adiponectin) adipokines that regulate the survival of eosinophils and their recruitment to the lungs [232, 233]. As mentioned above, visceral fat in obese patients releases the "adipokine" sCD26 into the circulation [88], but, as we have already been highlighting throughout this review, with proinflammatory or anti-inflammatory effects depending on the processed substrate: incretins or chemokines/substance P, respectively.

Obese persons are at risk of a number of comorbidities like type 2 diabetes mellitus (T2DM), a disease characterized by impaired production of incretins, with subsequently hyperglycaemia. Incretins (GIP, GLP-1, GLP-2) are well-known CD26 substrates that lose their function when they are processed. Inhibition of CD26 enzymatic activity avoids the degradation of these hormones, enhances the incretin effect, improves both the insulin secretion and the glucose uptake and lowers the glycosylated haemoglobin A1c levels. To achieve these goals, a new group of anti-hyperglycaemic drugs (CD26 inhibitors or gliptins) have come on the market, with sitagliptin, (Januvia®; Merck Sharp & Dohme Ltd) and vildagliptin (Galvus®; Novartis Europharm Ltd) (both approved by European Medicines Agency/EMA in 2007) as the first outpost (Table 4). Currently, there are several orally administered CD26 inhibitors that have been approved by agencies like the Food and Drug Administration (FDA) or EMA and are being used with satisfactory results as a second- or third-line medication in combination with other oral anti-diabetic drugs. Commercially available gliptins include the above-mentioned sitagliptin (Januvia®, Ristaben®) but also saxagliptin (Onglyza®), linagliptin (Trajenta®), alogliptin (Vipidia®) and vildagliptin (Galvus®, Jalra®, Xiliarx®) (Table 4). However, there is a controversial debate about the secondary effects on comorbidities (e.g., cardiovascular outcome, renal impairment, acute pancreatitis) that the long-term treatment with these long half-life inhibitors may have. These concerns are a result of several issues related to the great number of CD26 substrates linked or not to the immune system. Thus, the SAVOR TIMI-53 (saxagliptin) [234] trial detected a significantly increased rate for hospitalization due to heart failure, and a more recent study based on FAERS (US-FDA Adverse Event Reporting System) [235] is also consistent with this finding. In clear contrast, the TECOS trial (sitagliptin) [236] did not find an increased risk of heart failure.

More in accordance with the scope of this review, CD26 reversible inhibitors seem to increase the frequency of risk factors for asthma development/exacerbation like atopic sensitization, rhinitis or rhinovirus infection in T2DM patients [3]. Thus, a rapid review of clinical data published on the EMA web page (http://www.ema.europa.eu) supports increased risk of non-serious upper respiratory tract infections (e.g., viral nasopharyngitis, rhinitis, sinusitis) (Table 4), which would be in line with the costimulatory role of CD26. As Willemen and coauthors sustain, this increased risk of infections with CD26 inhibitors (~3 % cases) cannot be compared with the magnitude of the effects seen with biological agents like tumour necrosis factor inhibitors [237]. However, this effect should not be underestimated and must be added to the immune impairment caused by T2DM itself to increase the overall asthma development/exacerbation risk in these patients.

Other adverse drug reactions (ADRs) reported in association with gliptins and more associated with an inhibitory role of CD26 would be interstitial lung disease, hypersensitivity reactions (including anaphylactic responses or bronchial hyperreactivity) and skin and subcutaneous tissue disorders such as pruritus, angioedema, rash, urticaria, cutaneous vasculitis or more severe and rare skin conditions (Table 4). For example, Bullous pemphigoid [187, 238–240] is an autoimmune subepidermal disease with overproduction of eotaxin and eosinophilia that affects skin and mucosae. Therefore, the association between gliptins and bullous pemphigoid is in tune with in vivo studies in F344 rats showing that CD26 limits the eotaxin-mediated recruitment of eosinophils [187] or with the finding that oral administration of CD26 inhibitors promotes the allergic inflammation of the airways [45]. This means that CD26 could be part of a homeostatic mechanism to downmodulate airway inflammation mediated by T_{H2} and especially T_{H17}/T_{H1} cells important in some T_{H2}^{low} asthma phenotypes such as obesity-related asthma. Nevertheless, it should be noted that besides chemokines there are other CD26 substrates with implications on obesity and asthma like substance P. Inhaled substance P, but not bradykinin, enhances the airway response to bronchoconstricting agents in guinea pigs [241]. Substance P also favours allergen sensitization and bronchial inflammation, as observed in a mouse model of diet-induced obesity sensitized and challenged with OVA and treated with an antagonist of the substance P receptor (NK1-R) [242]. Therefore, expanded half-life in substance P caused by treatment with CD26 inhibitors in T2DM patients could increase certain obesity-related comorbidities such as asthma. In the same way, administration of sitagliptin in T2DM generates a temporary decrease in the percentage of peripheral blood Tregs that also could favour asthma prevalence in these patients [243]. In clear contrast, GLP-1-based therapies have anti-inflammatory effects in chronic inflammatory diseases including T2DM and asthma [244]. For example, in vitro studies have described that CD26 inhibitors induce a decrease of NLRP3 inflammasome, toll-like receptor 4 (TLR4) signalling

Table 4 DPP4 inhibitors registered for clinical use in EMA and adverse drug reactions identified during both the clinical and postmarketing surveillance stage

Active substance used as monotherapy	Proprietary name (company; date of EMA authorization)	Immune system and respiratory disorders, infections (frequency)[a]	Skin and subcutaneous tissue disorders (frequency)[a]
Sitagliptin	Januvia® (Merck Sharp & Dohme Ltd; 2007) Ristaben® (Merck Sharp & Dohme Ltd; 2010)	• Hypersensitivity, including anaphylactic responses (not known)[b] • Interstitial lung disease (not known)	• Pruritus (uncommon)[b] • Angioedema (not known)[b] • Rash (not known)[b] • Urticaria (not known)[b] • Cutaneous vasculitis (not known)[b] • Exfoliative skin conditions including Stevens-Johnson syndrome (not known)[b] • Bullous pemphigoid (not known)[b]
Vildagliptin	Galvus® (Novartis Europharm Ltd; 2007) Jalra® (Novartis Europharm Ltd; 2008) Xiliarx® (Novartis Europharm Ltd; 2008)	• Upper respiratory infection (very rare) • Nasopharyngitis (very rare)	• Urticaria (not known)[b] • Bullous pemphigoid (not known)[b] • Exfoliative skin conditions (not known)[b]
Saxagliptin	Onglyza® (AstraZeneca AB; 2009)	• Small decrease in the absolute count of peripheral blood lymphocytes • Upper respiratory infection (common) • Sinusitis (common)	• Pruritus (uncommon)[b] • Angioedema (rare)[b] • Rash (common)[b] • Urticaria (uncommon)[b] • Dermatitis (uncommon)
Linagliptin	Trajenta® (Boehringer Ingelheim International GmbH; 2011)	• Nasopharyngitis (uncommon) • Hypersensitivity (e.g., bronchial hyperreactivity) (not known) • Cough (uncommon)	• Angioedema (rare)[b] • Rash (uncommon)[b] • Urticaria (rare)[b] • Bullous pemphigoid (not known)[b]
Alogliptin	Vipidia® (Takeda Pharma A/S; 2013)	• Upper respiratory infection (common) • Nasopharyngitis (common) • Hypersensitivity reactions (not known)[b]	• Pruritus (common) • Rash (common) • Exfoliative skin conditions, including Stevens-Johnson syndrome, Erythema multiforme, Angioedema and Urticaria (not known)[b]

[a] Absolute frequencies of ADRs; very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to 1/100), rare (≥1/10,000 to 1/1000), very rare (<1/10,000) or not known (i.e., not estimated)

[b] Adverse drug reactions (ADRs) identified based on postmarketing surveillance

and IL-1β in macrophages via GLP-1 receptor [160]. Therefore, more studies are needed to clarify whether gliptins have an overall positive or negative role in T2DM patients with obesity-related asthma.

Concluding Remarks

CD26 is a relevant molecule in asthma for several reasons. The first one is because of its potential utility together with periostin to test the efficacy of the treatment with interleukin-13-neutralising monoclonal antibodies (e.g., Tralokinumab) in patients with severe uncontrolled asthma [245, 246]. Secondly, it is because of its multifunctionality nature, with both costimulatory and inhibitory roles in the immune system, apart from the high (but variable) CD26 levels in a subset of lymphocytes central to asthma: the $CD4^+$ T cells. Different authors have highlighted the inhibitory functions of this molecule relative to signalling mediated by cytokines and chemokines. A handful of chemokines important for $CD26^+$ T_{H2} cells during early-onset allergic or late-onset eosinophilic asthma includes chemotactic factors whose biological activity is reduced with low-intermediate

(eotaxin) or high (MDC, SDF1α) efficiency, whereas important chemokines for $CD26^{+}$ T_{H1} (I-TAC, IP-10, Mig) and $CD26^{high}$ T_{H17} cells (MDC), two Teff subsets relevant in obesity-related asthma, late-onset neutrophilic asthma or severe asthma, are inactivated with intermediate-high effectiveness. Therefore, CD26 could act as a "biological brake" by reducing the attraction of Teff cells at sites of inflammation (e.g., the bronchi). This means that CD26 inhibitors used in T2DM patients could lead to a higher persistence of unprocessed substance P or chemokines and exacerbation of $T_{H2}{}^{high}$ and especially $T_{H2}{}^{low}$ asthma. In conclusion, it is necessary to previously take into consideration the many existing questions regarding the biological functions of this enzyme before the therapeutic targeting of this molecule [247], as CD26 inhibitors could enhance the frequency of hospital admission amongst people with certain asthma phenotypes.

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