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REVIEW ARTICLE

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CD26: a key molecule in immune regulation and autoimmune diseases

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Abstract In this review, we focus on major aspects of the biology of CD26, a dipeptidyl peptidase IV (DPPIV)-containing surface glycoprotein with multiple functions. In particular, we discuss findings demonstrating that CD26/DPPIV has an essential role in immune regulation as a T cell activation molecule and a regulator of chemokine function. We also review recent studies that identify key cellular molecules that physically associate with CD26 and the potential consequences of their interaction, including those with clinically related implications. Furthermore, we present work suggesting a role for CD26 in the pathophysiology of immune-mediated disorders as well as autoimmune diseases. We present recent studies that investigate the potential role of CD26 as a molecular target for novel treatment modalities for immune-mediated diseases, with work involving the use of anti-CD26 monoclonal antibody, DPPIV inhibitors, and soluble CD26 molecules.

Key words Autoimmune disease · CD26 · Cell cycle arrest · Dipeptidyl peptidase IV (DPPIV) · T cell activation

Introduction

CD26 is a 110-kDa cell-surface glycoprotein with diverse functions, and is expressed on a variety of tissues, including epithelial cells and selected leukocyte subsets.[1,2] The isolated CD26 cDNA predicts a type II transmembrane protein comprising 766 amino acids, which belongs to the serine protease family, and has a short cytoplasmic tail of six amino acids.[3] As members of this family share the consensus motif Gly–Xaa–Ser–Xaa–Gly at the catalytic site,[4] the predicted CD26 amino acid sequence contains a putative catalytic site Gly–Trp–Ser–Tyr–Gly at positions 628–632, which fits the consensus sequence, with Ser-630 being assumed to be the catalytic residue.[3] Therefore, CD26 is a membrane-associated ectopeptidase with dipeptidyl peptidase IV (DPPIV) activity, capable of preferentially cleaving NH_2-terminal dipeptides from polypeptides with L-proline or L-alanine at the penultimate position. The predicted amino acid sequence of human CD26 illustrates approximately 85% homology with the rat DPPIV enzyme[5] and the mouse thymocyte activation molecule (THAM), the mouse homologue of human CD26.[6] Over the past decade, we have demonstrated that CD26 has a multitude of physiological roles, ranging from its role in immune regulation as a structure capable of transmitting T cell activation signals, to its role as a regulator of biological processes through its cleavage of biological factors.[7,8] In addition, accumulating evidence has shown that the CD26 molecule and CD26+ T cells play a role in the pathophysiology of autoimmune diseases, and in the maintenance and induction of chronic inflammation.[9–11] In this review, we study data focusing on the role of CD26 in the regulation of various aspects of the human immune system, as well as its role in immune-mediated disorders, including autoimmune diseases, and its potential suitability as a novel target for therapy.

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CD26 in immune regulation

CD26 expression is tightly regulated on human T lymphocytes, with its density being markedly elevated following T cell activation.[1,10,12,13] At the resting state in the peripheral blood, CD26 is preferentially expressed on the helper/memory T cell population.[14] High CD26 cell surface expression is correlated with the production of Th1-like cytokines

by T-cell clones, and CD26 expression is induced by stimuli that favor the development of the Th1 response.[15] As well as its enhanced expression on activated T cells, various lines of evidence have converged to demonstrate that CD26 is functionally associated with T cell signal transduction processes, which are capable of transmitting signals relating to T cell activation. CD26 is able to conduct interleukin-2 (IL-2)-dependent co-mitogenic signals in conjunction with activation through the CD3/T cell receptor complex or the CD2 pathway of mature human T lymphocytes when cross-linked with solid-phase immobilized antibodies.[12] On the other hand, CD26 is mostly found on the surface of medullary thymocytes, the population of relatively mature thymocytes expressing high level of CD3.[16] Unlike the case of mature peripheral blood T cells, the ability of CD26 to mediate co-mitogenic signal in thymocytes is restricted to the CD3 pathway only, and does not involve CD2-induced activation. Hence, these findings suggested that CD26 might have a role in thymic differentiation and maturation via the differential engagement of the CD3 pathway.

Meanwhile, anti-CD26 antibody binding results in a decrease in CD26 surface expression due to its internalization, which is associated with the enhanced tyrosine phosphorylation of such key signaling molecules as CD3-ζ and $p56^{lck}$, as well as an increased proliferative response to anti-CD3 and anti-CD2 stimulation.[17–19] Moreover, we have recently demonstrated that CD26 localizes into lipid rafts, and targeting of CD26 to the rafts is necessary for signaling events through CD26.[20] Importantly, the aggregation of CD26 by anti-CD26 monoclonal antibody (mAb) cross-linking also causes the coaggregation of CD45 into rafts.

Effect of DPPIV enzyme activity on CD26-mediated T cell activation

Studies using various experimental approaches have indicated that DPPIV enzyme activity has a role in CD26-associated T cell activation. Multiple in vitro studies using chemical inhibitors of the DPPIV activity of CD26 have shown that DPPIV plays a key role in T cell activation. DPPIV inhibitors inhibit antigen-specific T cell proliferation and IL-2 production,[21] mitogen-induced T cell proliferation and immunoglobulin production,[22] and DNA synthesis and the production of interleukin (IL)-2, IL-10, IL-12, and interferon-gamma, while enhancing the secretion of the immunosuppressive cytokine transforming growth factor (TGF)-β1 by pokeweed mitogen-stimulated T lymphocytes.[23] Moreover, blockage of DPPIV activity by DPPIV inhibitors results in the clinical improvement of experimental autoimmune encephalomyelitis, while increasing the secretion of the immunosuppressive cytokine TGF-β1.[24] Inhibition of DPPIV activity also impairs host cytotoxic T lymphocyte responses and abrogates acute rejection of cardiac allografts in rat recipients, leading to prolonged allograft survival.[25] In two arthritis models which shared several pathological features associated with rheumatoid arthritis (RA), specific DPPIV inhibitors suppress arthritis, suggesting that inhibition of DPPIV activity is a therapeutic strategy for RA treatment.[26]

Recently, other researchers as well as ourselves have shown that CD26/DPPIV regulates the immune system by cleaving selected chemokines at the N-terminus to alter their receptor specificities and biological functions, as well as its direct involvement in T cell function. Among the increasing list of candidate substrates for DPPIV-mediated cleavage are such biological factors as CCL3 (MIP-1α isoform LD78β), CCL4 (MIP-1β), CCL5 (RANTES), CCL11 (eotaxin), CCL22 (MDC), CXCL6, CXCL9, CXCL10, CXCL11, and CXCL12 (SDF-1α).[2,13,27–31]

Using the CD26-negative human T cell leukemia line Jurkat, we have established stable CD26 transfectants to further investigate the role of CD26 and its DPPIV enzyme activity in T cell activation. Wild-type CD26+DPPIV+ Jurkat transfectants consistently produce higher level of IL-2 than the mutant CD26+DPPIV or vector-only transfectants following stimulation with a combination of anti-CD3 and anti-CD26 mAbs, or with stimuli not directly involving CD26, such as anti-CD3 and phorbol esters.[32] Meanwhile, experiments using either recombinant soluble CD26 (sCD26) that contains DPPIV activity (sCD26+DPPIV+) or soluble CD26 mutated at the DPPIV active site (sCD26+DPPIV−) also demonstrated that the presence of DPPIV enzyme activity enhances peripheral blood T cell proliferation induced by the recall antigen tetanus toxoid.[33] Regarding the above mechanism, our recent work showed that the exogenously added sCD26, and particularly its DPPIV activity, directly affects CD14+ peripheral blood monocytes in the early stages of the immune response to recall antigens through its ability to up-regulate expression of the co-stimulatory molecule CD86 on monocytes.[34]

CD26-associated molecules

Recently, we demonstrated that CD26 interacts physically and functionally with several molecules which play key roles in T cell function. CD26 is co-modulated on the T cell surface with CD45, a membrane-linked tyrosine phosphatase which is critical to T cell signal transduction, while anti-CD26 mAbs are capable of co-precipitating CD45 from T cell lysates.[18] Furthermore, anti-CD26 mAb binding leads to co-localization of both CD26 and CD45 into lipid rafts; a process that involves CD26 binding to the cytoplasmic domain of CD45.[20] Since CD45 regulates the phosphorylation status and activities of proteins involved in T cell signal transduction cascades,[35,36] the augmented tyrosine phosphorylation of the CD3-ζ chain and increased $p56^{lck}$ tyrosine kinase activity associated with antibody-mediated CD26 internalization may result from CD26–CD45 interaction.

Another molecule that binds to cell-surface CD26 is the mannose 6-phosphate/insulin-like growth factor II receptor (M6P/IGFIIR), with the M6P residues in the CD26 carbohydrate moiety being critical for this interaction.[37] The activation of peripheral blood T lymphocytes results

in the mannose 6-phosphorylation of CD26. In addition, antibody-mediated cross-linking of CD26 induces co-localization of CD26 with M6P/IGFIIR, along with capping and internalization of CD26 and subsequent CD26-mediated T cell co-stimulation.[37] Meanwhile, the CD26–M6P/IGFIIR association appears to be essential for the monocyte–T cell interaction which is critical in immune responses to recall antigens, as it plays a role in the transportation of sCD26 into monocytes, leading eventually to increased expression of the co-stimulatory molecule CD86.[34] More recently, we showed that sCD26 mediates enhanced transendothelial migration, an effect that requires its intrinsic DPPIV enzyme activity.[38] Moreover, sCD26 directly targets endothelial cells, and M6P/IGFIIR on the endothelial cell surface acts as a receptor for CD26. Our results suggest that sCD26 influences T cell migration through its interaction with M6P/IGFIIR.

CD26 also physically associates with adenosine deaminase (ADA) as the ADA-binding protein.[39,40] ADA is involved in purine metabolism, while its key role in lymphocyte biology is indicated by the fact that ADA deficiency is a cause of severe combined immunodeficiency disease.[41] Meanwhile, adenosine has multiple functions, including the inhibition of T cell activation, particularly in the absence of cell-surface ADA. On the other hand, cells expressing ADA and CD26 on the surface display greater resistance to adenosine-mediated inhibition.[42] Therefore, surface-bound ADA may be involved in immune regulation via its physical association with CD26 by deaminating extracellular adenosine and activating T cells.[13,42]

Recent work has also shown that CD26 physically and functionally associates with the chemokine receptor CXCR4 on the surface of human peripheral blood lymphocytes.[43] CD26 co-localizes with CXCR4 on T and B cell lines, while the two molecules co-immunoprecipitate from cellular membranes. Down-regulation of CXCR4 induced by its physiological ligand CXCL12 (SDF-1α) also results in co-internalization of CD26 on lymphocytes. Furthermore, treatment with SDF-1α induces the formation of pseudopodia in which both CD26 and CXCR4 co-localize, and in which ADA is absent. Since CD26 is capable of cleaving SDF-1α and thereby affecting its biological function,[28,29,44] the CD26/CXCR4 complex may be a functional unit allowing CD26 to directly modulate SDF-1α activity.

CD26 and the cleavage of cytokines and chemokines

Recent studies have demonstrated that CD26/DPPIV cleaves a number of cytokines and chemokines to alter their biological functions by altering their chemotactic potency, impairing their signaling effects, and modifying their receptor specificity. Initial studies by Oravecz et al.[27] demonstrated that the receptor specificity of CCL5 (RANTES) is altered by DPPIV-mediated cleavage, because signaling through CCR1 and CCR3 by RANTES is abolished by the 2 amino acid-truncation mediated by CD26/DPPIV, while signaling through CCR5 is not affected. Further studies showed that CD26/DPPIV-mediated cleavage of RANTES influences its activity in monocyte chemotaxis and HIV-1 infection.[45] Work done subsequently by various investigators, including ourselves, further showed that an emerging aspect of CD26 biology is the ability of its intrinsic DPPIV enzyme activity to cleave selected chemokines to alter their biological effects. For example, the chemotactic and anti-HIV activities of mature SDF-1α are both abolished by cleavage of membrane-bound as well as soluble CD26/DPPIV.[28,29,44] In addition, CCL11 (eotaxin), an important mediator of allergic reactions due to its ability to attract eosinophils, Th2 lymphocytes, and basophils, is a substrate for CD26/DPPIV. DPPIV-cleaved eotaxin exhibits reduced chemotactic activity for eosinophils, and impaired binding and signaling via its receptor CCR3, while differentially regulating the chemotactic and antiviral properties of intact eotaxin.[46] Other chemokines which have been shown to exhibit altered receptor specificity and biological activity following CD26/DPPIV-mediated cleavage include CCL22,[47,48] CCL3,[30,49] and the interferon-inducible chemokines.[50]

Role of CD26 in autoimmune diseases and other immune-mediated disorders

Patients with autoimmune diseases such as multiple sclerosis, Grave's disease, and RA have been found to have increased numbers of CD26+ T cells in inflamed tissues as well as in their peripheral blood.[9–11,51] In addition, enhancement of CD26 expression in these autoimmune diseases may correlate with disease severity.[52–54] These findings imply that CD26+ T cells play a role in the inflammation process and subsequent tissue damage in such diseases. Moreover, we and others have shown that T cells migrating through endothelial cell monolayers in vitro express high levels of CD26,[55,56] and the fact that chemokines play a key role in T cell migration[57–60] supports the notion that CD26/DPPIV may interact with chemokines.

Serum sCD26 was initially detected by DPPIV enzyme activity. DPPIV levels in human serum have been examined in patients with various diseases, including autoimmune diseases, malignancies, infectious diseases, and psychiatric disorders.[2] Serum DPPIV activity increased markedly in parallel with the acceleration of lymph node swelling and anti-nDNA antibody production in mice of the autoimmune MRL/MP–lpr/lpr strain.[61] In contrast, decreased serum DPPIV activity was found in the New Zealand Black mouse, and in patients with systemic lupus erythematosus (SLE) and RA.[62] To determine the role of soluble CD26 in the pathophysiology of patients with SLE, we measured levels of sCD26 and its specific DPPIV activity in serum.[63] Serum levels of sCD26 and its specific DPPIV activity were significantly decreased in SLE and were inversely correlated with SLE disease activity index score, but not with clinical variables or clinical subsets of SLE. A close correlation between sCD26/DPPIV and disease activity was observed in a longitudinal study. Serum levels of sCD26 may

be involved in the pathophysiology of SLE, and appear to be useful as a new disease activity measure for SLE. Recently, Cordero et al.[64] reported that sCD26 in patients with RA was significantly reduced, and was related to disease activity. We have also measured sCD26/DPPIV levels in sera from patients with RA and found a significant decrease in sCD26 and its specific DPPIV activity.[63]

CD4+ lymphocytes in patients with AIDS have an intrinsic defect in their ability to recognize and respond to recall antigens some time before a reduction in the total number of CD4+ cells occurs.[65,66] The response to recall antigens is clearly a property of CD4+CD26+ T cells, since this is the only helper population known to proliferate in response to soluble antigens, and to induce both MHC-restricted cytotoxic T lymphocytes capable of killing virus-infected target cells and B cells to secrete immunoglobulins.[14] In this regard, a selective decrease in CD26+ T cells has been reported in HIV-1-infected individuals prior to a general decrease in CD4+ T cells.[67,68] Moreover, Tat, a regulatory protein encoded by the HIV-1 genome,[69] has been shown to suppress the response of human peripheral T cells to soluble antigens.[70] It has also been suggested that Tat can bind to CD26 and partially inhibit DPPIV enzyme activity.[71] We have shown that the DPPIV enzyme activity of plasma sCD26 was low in HIV-1-infected individuals, and was inversely correlated with HIV-1 RNA, and that the in vitro addition of recombinant sCD26 could enhance purified protein derivative (PPD)-induced lymphocyte proliferation.[72] These results suggest that the specific DPPIV enzyme activity of plasma sCD26 in HIV-1-infected individuals contributes to the immunopathogenesis of HIV infection.

Taken together, the above findings suggest that CD26/DPPIV plays an important role in the pathophysiology of autoimmune diseases and other immune-mediated disorders. Moreover, in vivo recombinant sCD26 supplementation in immunodeficient patients with decreased serum sCD26/DPPIV may be of use in restoring the immune responsiveness.

CD26 as a potential therapeutic target in autoimmune diseases

We recently conducted studies to investigate the potential role of CD26 as a novel treatment target in autoimmune diseases. We demonstrated that binding of soluble anti-CD26 mAb (1F7) inhibits the proliferation of CD26 Jurkat transfectants and T cell clones derived from human peripheral blood.[73] Moreover, anti-CD26 binding results in cell cycle arrest at the G1/S checkpoint, which is associated with increased $p21^{Cip1}$ protein and mRNA levels. Finally, we showed that extracellular signal-regulated kinase (ERK) pathways appear to play a role in the enhancement of $p21^{Cip1}$ expression following anti-CD26 mAb treatment.[73]

Activated memory T cells express high levels of CD26, and this phenotype of late-memory T cells is associated with increased antigen sensitivity both in vivo and in vitro.[74] Moreover, CD26+ T cells play a role in the pathophysiology of various autoimmune diseases, suggesting that CD26+ T cells function as effector T cells. In view of these findings, CD26 can potentially be a target for immunotherapy. In fact, anti-CD26 treatment was reported to be effective in decreasing the incidence of steroid-resistant acute graft-versus-host disease (GVHD) after allogeneic bone marrow transplantation,[75,76] although the precise mechanism involved in these clinical results has not yet been elucidated. Our data therefore suggest that cell cycle regulation of activated T cells via CD26 might be useful for controlling acute GVHD by inhibiting cellular proliferation. Taken together with the observation that transfection of the $p21^{Cip1}$ gene enhanced cyclosporin A-mediated inhibition of lymphocyte proliferation,[77] anti-CD26 mAb therapy may serve as an alternative strategy to induce immunosuppression, and one that is potentially less toxic than the side-effects currently seen with conventional agents.

The ability to inhibit T cell proliferation and induce G0/G1 arrest through the use of anti-CD26 mAb may therefore lead to the eventual development of new reagents targeting CD26+ activated T cells, including immunotherapy of allogeneic organ transplants resistant to current treatment modalities. Furthermore, given its enhanced expression and its potential role in the pathophysiology of autoimmune inflammatory diseases, CD26-targeted treatment may similarly prove to be effective in these clinical settings.

Conclusion

In this review, we focused on various aspect of CD26 in immune regulation and immune-mediated disorders. Moreover, our recent studies suggest that CD26 may be an appropriate target for novel treatment modalities for immune-mediated disorders such as RA and acute GVHD. In view of its multifunctional roles in immune function, future therapeutic strategies targeting CD26 and its DPPIV enzyme activity may be of potential value in the clinical setting.

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