

Review Article

Immunomodulatory Activity of DPP4

Mamgain S*, Mathur S and Kothiyal P

Department of Pharmaceutical Sciences, Shri Guru Ram Rai institute of Technology & Sciences, India

*Corresponding author

Mamgain S, Department of Pharmaceutical Sciences, Shri Guru Ram Rai institute of Technology & Sciences, Dehradun, Uttarakhand, India, Email: mamgainwati14@gmail.com

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Abstract

Dipeptidyle peptidase (DPP4) is the enzyme which is known to break down two gut hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) known as incretins effect. Beside this DPP4 plays potential role in modulating immune system. It causes proliferation of T cell by binding with adenosine diaminase (ADA) through co-stimulatory mechanism. Within immune system DPP4 exert mainly stimulating effect on T cells, B cells, natural killer cell, DNA synthesis and release of TGF β . Evidence from experimental studies suggest the potential role of DPP4 in various inflammatory disease and increased risk of cancer. Inhibitor of DPP4 is novel treatment for diabetes mellitus type2 which inhibit DPP4. DPP4 plays crucial role in immune modulation therefore its prolong inhibition results in implication in immune system and increase risk of developing tumor. Therefore these classes of drugs prescribed with a caution. Further studies needed for more clarification.

Keywords

- Dipeptidyle Peptidase 4
- CD26
- Immunomodulatory effect
- ADA Co-stimulatory mechanism

INTRODUCTION

Dipeptidyle peptidase 4 (DPP-4) is the enzyme normally present in liver hepatocyte, kidney and intestine responsible for cleavage of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP) known as incretin effect. DPP4 shows immunomodulatory activity. DPP4 inhibitors are widely used for the treatment of type 2 diabetes mellitus by augmenting incretin signaling pathway [1]. Therefore long term inhibition of DPP-4 may play potential pathophysiological role in number of inflammatory disorders [2,3].

DPP 4 is also known as adenosine diaminase binding protein (ADBP) or T cell activation antigen CD26 [4]. It is 766 glycosylated multifunctional and is widely distributed serine protease it acts by cleaving the N terminal dipeptide after proline containing peptide. It act through various mechanism [5-7].

- Proliferation of T cell by co-stimulation mechanism.
- Involving in interaction with extracellular matrix.
- Influencing proteolysis by activation and inactivation of many peptide lead to influence HIV, diabetes as well as immune system (Figure 1)

DPP4 SUBSTRATE

DPP4 bind to several substrates which include Neuropeptide Y, Interleukins, incretin, cytokines, RANATES etc.

DPP4 in immune system

Experimental result from study of allogeneic bone marrow transplantation demonstrate decrease number of CD26 cell

which involve in T cell proliferation through CD3 and CD28 pathway results in mature thymocyte similar to medullary thymocyte or cord T cell. DPP-4 ectopeptide present in plasma level of T lymphocyte and part of T lymphocyte characterize as memory T cell expressed on CD4 or CD8 hemoprotein as well as on thymocyte B cell [8], cytokines [9]. It has been shown CD26 plays crucial role in T cell proliferation by co-stimulation mechanism. In addition CD26 also regarded as activation marker of B lymphocyte and natural killer cells [8]. Immunoregulating cytokines part of immune system has been shown to substrate of DPP4 [3]. Hence DPP4 have major impact on immune system.

Adenosine diaminase (ADA) binding

Adenosine diaminase (ADA) catalyse deamination of adenosine to inosine in a purine catabolism pathway. ADA is

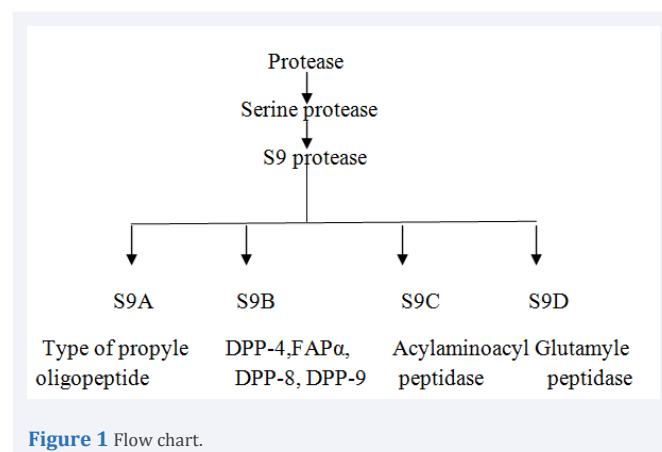


Figure 1 Flow chart.

ectoenzyme which synthesizes by AMP dephosphorylation and taken by *S*-adenosylhomocysteine (SAH) to the extracellular space where it forms a complex with CD26 mediating the immune response through T cell activation. There are various forms of ADA, ADA₁ bind to CD26 [10]. Neither adenosine activity nor enzymatic activity is required for binding of CD26 with ADA. ADA1 is isoform whose deficiency may be associated with [severe combined immunodeficiency](#) (SCID).

ADA depend CD26 mediated signaling

ADA binds to its receptor [A_{2B}] expressed on dendritic cells and mediates T cell activation through co-stimulation by CD26. When the ectoenzyme binds to its receptor A_{2B} on dendritic cells, it results in increased cross-linking of CD26. Cross-linking of CD26 causes co-precipitation of CD26 and CD45RO on lipid rafts. Subsequently, through interaction of CD26 with the cytoplasmic domain d₂ of CD45RO, it promotes dephosphorylation of the C-terminal of regulatory domains of Src kinases such as Lck and Fyn, activating them. Activated Lck binds to the cytosolic domain of CD4 and CD8 and phosphorylates immunoreceptor tyrosine-based activation motifs (ITAM) of CD3ζ, allowing ZAP-70 (zeta chain associated protein kinase 70, normally expressed near the surface membrane of T cells) to bind to phosphorylated ITAM. Thus, Lck activates ZAP70. ZAP70, through phosphorylation of LAT, promotes activation of the ERK pathway and PLCγ. The cross-linking of ADA and CD26 induces a synergistic effect on calcium mobilization triggered via the TCR/CD3 complex. Therefore, the co-stimulatory signal triggered via CD26-ADA interaction potentiates the TCR/CD3 engagement during T cell activation.

The novel co-stimulatory intracellular interaction

Recently, it has been discovered that co-stimulatory effects through CD26 on the T cell surface are promoted by ecto-ADA co-localizing with A_{2B} adenosine receptors expressed on antigen-presenting cells (APC) surface. The novel co-stimulatory intracellular interaction involves a trimolecular interaction of CD26, ADA, and A_{2B} receptors present on dendritic cells. Co-stimulation through cross-linking of CD26 and ADA results in the release of IL6, IFNγ, and TNF α secretion [11].

B LYMPHOCYTE

The presence of CD26 on B lymphocytes has always been controversial. A study using anti-CD26 antibodies recognized an epitope of DPP4, indicating the presence of CD26 on T lymphocytes. According to experimental studies, B cell expression was studied in healthy individuals and in patients with CVID (disease caused by B cell dysfunction). CD26 was detected with the help of a specific enzyme substrate. After stimulation with pokeweed mitogen (PWM) or Staphylococcus aureus, it shows the proliferation of CD26 nearly the same. Treatment with DPP4 inhibitors on PWM and Staphylococcus aureus-stimulated B cells in a study shows DNA synthesis inhibition in a dose-dependent manner. All observations signify that DPP4 is not only an activation marker of T cells and NK (natural killer) cells but also of B cells [8].

CHEMOKINES

Stimulation of human T cells by pokeweed mitogen (PWM) shows a decrease in mRNA expression of cytokines [12].

Chemokines related to cytokines play a role in chemotaxis phenomena (migration of T lymphocytes) exerting its signaling action through the N-terminal, which is cleaved by CD26. Results in impaired signaling pathways in the immune system. There are various types of chemokines which involve in the migration of eosinophils on paracytes after processed by CD26, losing their ability to work in the immune system. RANTES (regulated on activation normal T cell expressed and secreted) processed by CD26 becomes more than ten times lower in signaling binding. CCR1 and CCR3 result in lowering of chemotactic properties. Stromal cell derived factor 1 present on the surface of CXC chemokines loses its efficacy due to manifestation in signaling pathways of CXC chemokines. Cleavage of the N-terminal results in shortening of macrophage-derived chemokines, which impairs its effect on Gly-pro² and Try³Gly⁴, leading to an increase in substrate specificity as compared to before. Therefore, CD26 plays a crucial role in transduction of cytokines involved in various immune regulating systems. A study also shows the DPP4 role in the production of IL2, IL6, IL10, and TNFα.

T LYMPHOCYTES

- The main role of CD26 in T cell activation is determined by finding monoclonal antibodies against T cell activating agents, resulting in the release of interleukins and proliferation of CD4 and CD8 T cells.
- IFN monoclonal antibody shows proliferation of CD26, which involves a cascade of reactions resulting in modulation of activated T cells.
- CD45 is co-precipitated with CD26 in T cell lysates. CD45 plays an effective role in signaling T cell receptors and leads to a modulating effect of CD26.
- The collagen binding activation of CD26 on T cells leads to produce co-stimulatory signals [13].

ROLE IN DNA SYNTHESIS AND TGFβ

CD26 plays a crucial role in DNA synthesis, evident by a study using phytohemagglutinin and Co-enzyme A stimulated assay. Inhibition of DPP4 results in the release of TGF β, which may cause immune suppression. TGFβ is transforming growth factor β, which involves regulation and production of immune cells. Its release results in manifestation in the immune system [14] (Figure 2).

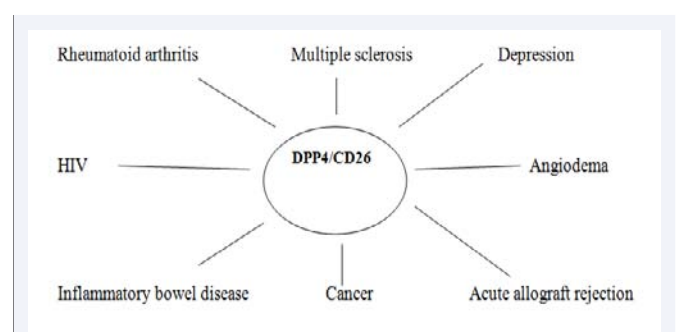


Figure 2 Role of DPP4 in Various Immune Related Diseases.

Table 1: Various substrate of DPP4.

| SUBSTRATE | EFFECTS |
|---------------------------|--|
| Aprotinin | Inhibits trypsin and related proteolytic enzymes |
| Bradykinin | Causes vasodilates and increases vascular permeability |
| β - Casomorphin -2 | Opioid - like effects on the CNS |
| Chromogranin | Modulates the neuroendocrine function |
| Endomorphin -2 | Endogenous opioid - peptides |
| Eotaxin | (or CCL11) Chemotactive for eosinophils, implicated in asthma |
| GCP - 2 | (or CXCL6) Recruits neutrophils |
| GHRH | Stimulates GH production and release by binding to the |
| GRP | Elicits gastrin release and regulates gastric acid secretion and motor function |
| IGF - 1 | Allows childhood growth and anabolism in adults. Insulin counter - regulatory |
| Protactin | Allows lactation, regulate fertility and is counter - regulatory |
| IL - 2 | Major role in specific immunity |
| IL - 1β | Major regulator of inflammation, cell proliferation, differentiation, apoptosis |
| IP - 10 | (or CXCL10) Attracts leukocytes to the endothelium. Involved in bone marrow colony formation and angiogenesis |
| MCP - 1, - 2, - 3 | (or CCL2) Recruits leukocytes to sites of tissue injury, infection, and inflammation |
| RANTES | (or CCL5) Recruits leukocytes into inflammatory sites |
| SDF- 1α, - 1β | Stimulates chemotaxis, stem / progenitor cell mobilization and homing |
| NPY | Regulation of energy balance, memory and learning |
| Substance P | Neuroransmitter and neuromodulator, role in neurogenic inflammation |
| PYY | Reduces appetite, inhibits gastric motility and increase water and electrolyte absorption in the colon |
| PHM | Causes vasodilates and possibly act as a neurotransmitter |
| GLP - 1 | Promotes insulin secretion, slowing gastric emptying, reducing appetite |
| GLP - 2 | Intestinal growth and function, reduction in bone resorption, neuroprotection |
| GIP | Inhibits GI motility and acid secretion. Stimulates insulin secretion and promotes fatty acid metabolism |

HUMAN IMMUNE DEFICIENCY VIRUS

There were many hypothesis of CD26 associated with HIV in past but it is now confirmed by study that CD26⁺ cell are more sensitive towards HIV infection in comparison to CD26⁻ cells. CD26 interact with TAT protein which is trans activated HIV protein. Sialylation of CD26 indicates its interaction with TAT protein and Hypersialylation of CD26 contributes to the fusion of HIV particle with its host.TAT protein on interaction with CD26 inhibit DPP4 mediated T cell proliferation through co-stimulation result in diminishing immune response.

Another is gp120 an envelope glycoprotein protein of HIV particle interact with CD26 through C3 region while interact with CD4 through V3 loop results in loss of binding of ADA to CD26 affecting immune response. High level of ADA found in HIV infected patient. Beside these two protein chemokines plays role in HIV [15]. RANATES is known to inhibit HIV infection via its

capability of binding with CCR5.RANATES processed by CD26 is compared with intact RANATES with macrophage tropic activity found processed RANATES are more effective against HIV1.In early stage of HIV highly expressed CD26 would be beneficial because of M tropic CCR5. In later stage of HIV infected patient CD26 diminish immune response and enabling person more susceptible for HIV due to abolish protective effect of SDF(stromal cell derived factor)1α [13].

CANCER

The relation of DPP4 to cancer biology is extremely complex and has been repeatedly reviewed recently.DPP4 regulate apoptosis, immune regulation, antiproliferative and anticogenic action for cancerous cell thereby modulating development of cancer. Several studies evident downregulation of DPP4 in ovarian cancer, which resulting in increase of ductal cell turnover and inducing ductal mataplasty by intacting β cell and its function. DPP4 inhibitor Sitagliptin may contribute to pancreatic cancer. Sitagliptin use in the treatment diabetes mellitus type 2 act by inhibiting action of DPP4 which causes cleavage of GLP2. GLP2 have proliferative effect on intestinal cell. Therefore DPP4 inhibition exerted tumor promoting effect on intestinal cancer cell invitro [3].

Acute allograft rejection

CD26 shown to decrease immune suppression investigated in TX cardiac recipient patient by using DPP4 inhibitor. DPP4 inhibitor prolong TX cardiac recipient survival which signify role of CD26 in immune regulation [16].

Inflammatory bowel disease

Inflammatory bowel disease caused by increase in number of inflammatory cell [17]. Role of DPP4 in IBD is define by investigation supporting high expression of CD26 on T lymphocyte as compared to control. In laboratory dextran sulphate sodium induced colitis in DPP^{+/+} and DPP4^{-/-} mice shows to exaggerate inflammatory response as compared to DPP^{+/+} mice. IBD and colitis can be use as *in vivo* model for evaluating immune modulatory activity of DPP4 [18].

Rheumatoid arthritis

Rheumatoid arthritis is a disease caused by increase in a number of lymphocyte in synovial fluid. Role of DPP4 is investigated by using two animal model of Rheumatoid arthritis

1) Collagen induced arthritis

Table 2: Tissue distribution of human CD26.

| ORGAN | CD26 ⁺ CELLS |
|----------------|--|
| Kidney | Proximal tubule epithelium,glomerulus endothelia |
| Liver | Bile canaculi,bile duct epithelia |
| Skin | Fibrocytes |
| Parotid gland | Acinus epithelia |
| Spleen | Sinus-lining cell |
| Adrenal gland | Zone reticularis |
| Prostate gland | Epithelia |
| Lungs | Endothelia |

2) Alkyldiamine induced arthritis

DPP4 inhibitor shows anti arthritic effect by suppressing collagen induced arthritis as well as alkyldiamine arthritis indicating role of DPP4 in immune regulation [19]. Specific serum activity of DPP4 is decrease in Rheumatoid arthritis patients [20].

Depression

A study of DPP4 inhibitor demonstrate the role of DPP4 in depression shows that

- Major depression is associated with decrease level of DPP4
- Antidepressant does not have any effect on DPP4 activity
- Low DPP4 serum level is important marker in depression [21].

Angiodema

Angiodema is a disease caused by swelling of skin, mucous membrane or both including upper respiratory and intestinal epithelial linings. It is caused by increase in permeability of subcutaneous capillaries which leads to extravasation of plasma and ephemeral swelling [22]. ACE (Angiotensin converting enzyme) plays a primary role in degradation of Bradykinin which results in increased vascular permeability which in turn causes Angiodema. Use of ACE inhibitor results in decreased degradation of Bradykinin but DPP4 secondary pathway increases its degradation. DPP4 inhibitor along with ACE inhibitor results in decrease in degradation of Bradykinin which causes Angiodema. For study purposes one patient of RA on immunosuppressant drugs along with two patients from heart transplantation and one patient with history of malignancy forma comprehensive study group. Angiodema is found to be associated with malignancy as well as in autoimmune disorder [23].

Multiple sclerosis

Multiple sclerosis is demethylating disease caused by abrupt activation of immune system [24]. In multiple sclerosis activated CD4, Th1 and various cytokines are found on myelin based protein (MBP). A study shows that CD26 present on myelin based protein, CD4 and T cell clones plays important role in regulation of T cell clones. Hence DPP4 inhibitor is found to be effective in treatment of multiple sclerosis and it can serve as in vivo model for DPP4 inhibitor [25].

Evidence from preclinical and clinical studies

DPP4 is widely expressed on kidney, liver, small intestine and blood cell of rat. DPP4 activity is determined by using DPP4 inhibitor in invitro studies which substantiated inhibition in T cell proliferation whereas invivo studies using Bovine Serum Albumin (BSA) with DPP4 inhibitor has shown to decrease level of antibody formation followed by decrease in serum enzymatic activity of DPP4 [26].

Hepatitis is one of the infectious disease for which vaccine is available but sometimes incompetence of vaccine is seen in a person due to low level of antibody after vaccination CD26/DPP4 increase T cell proliferation while increasing serum level of DPP4 at the same time [27]. After hepatitis B vaccine the serum level of

DPP4 found to increased level of CD45 (which is classic marker of T cell activation) in responder patient [10].

CONCLUSION

Although both pre-clinical and clinical studies have shown potential role of DPP4 therapy in diabetes but beyond DPP4 effect in regulation of energy homeostasis, its role in various immune related disorders has been implicated. Various experimental findings have suggested the role of DPP4 in T cell, B cell and natural killer cell activation. Despite this there is increased risk of tumors after prolonged use of DPP4 inhibitors as indicated by experimental studies. Therefore DPP4 inhibitors in clinical practice are still in question because of the safety issue. Based on above stated arguments we can aver that more statistics be collected and studied before starting human testing.

FUTURE PROSPECTS

Further studies are needed for more clarification about role of DPP4 in immune response to protect dangerous effect of using DPP4 inhibitor and hence should be given with some degree of caution in patient to safeguard their lives.

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