Cellular expression of CD26/dipeptidyl peptidase IV

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ABSTRACT

Dipeptidyl peptidase 4 (DPP4), a serine protease expressed on luminal and apical cell membrane, is identical to the lymphocyte cell surface protein CD26. DPP4 rapidly deactivates hormones and cytokines by cleaving their NH₂-terminal dipeptides. Its functions are based on membrane digestion and/or binding of bioactive peptides, signal molecules, and extracellular matrix components. The soluble form is also present in body fluids such as serum, urine, semen, and synovial fluid. The extremely broad distribution of CD26/DPP4 indicates its divergent roles depending on cell type and activated conditions. The cellular localization was earlier examined by enzyme histochemistry and subsequently by immunohistochemistry. Although immunohistochemical analyses are higher in specificity and easier to use at electron microscopic levels than enzyme histochemistry, the immunoreaction is considerably affected by the animal species, types of tissue sections, and specificity of antibodies. Understanding of the functional significance and advancement of its clinical use (diagnosis and treatment of diseases) require precise information on the cellular distribution including subcellular localization and pathological changes. This short review summarizes in particular immunohistochemical findings on CD26/DPP4.

INTRODUCTION

Dipeptidyl peptidase IV (DPP4, EC 3.4.14.5), a glycoprotein composed of 766 amino acids, possesses a dipeptidyl (amino) peptidase activity in its extracellular domain. It has only six amino acids at the cytoplasmic position. Membrane-bound or released forms of this enzyme are associated with two processes. First, DPP4, a serine exopeptidase, cleaves N-terminal dipeptides of proline or alanine-containing peptides including incretins, e.g., glucagon-like peptide (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), and neuropeptides such as substance P and vasoactive intestinal peptide (VIP). Thus, DPP4 inhibitors which prevent the degradation of incretins have led to the development of new drugs for diabetes. Second, by breaking down ligands such as peptide signals, growth factors, cytokines, and extracellular matrix (ECM), DPP4 can reduce or change cellular responses induced by these ligands, being involved in extracellular communication and cell migration. DPP4 has been found to be identical with a lymphocyte surface antigen CD26, which regulates mainly T cell development and stimulation. CD26/DPP4 has also been termed an adenosine deaminase binding protein or adenosine deaminase complexing protein. It shows an extremely broad expression in a variety of cells (Mentzel et al. 1996), suggesting divergent functions according to cells and tissues. Simultaneously, this characteristic may make it hard to simply understand its functional significance.

The cellular localization of CD26/DPP4 was first investigated by enzyme histochemistry and later by immunohistochemistry. However, it is a fact that the localization has shown significant differences be-
between the two histochemical methods in some cases, for example, in the salivary glands (Sahara and Suzuki 1984). Its predominant localization is largely classified into exocrine glands (salivary glands secreting saliva and liver secreting bile), absorptive tissues (intestine and kidney), vascular endothelium, and lymphocytes. The liver expresses CD26/DPP4 along the biliary tree from the bile canaliculi to large bile ducts (Tarantola et al. 2012); salivary glands also display its localization along the excretory system (Sahara and Suzuki 1984). CD26/DPP4 thus is listed as a histochemical marker of bile canaliculi and salivary excretory ducts. In the present short review, we summarize the cellular localization of CD26/DPP4 in mammals.

**Fibroblasts**

A subpopulation of human and murine dermal fibroblasts express CD26/DPP4. CD26+ fibroblasts, which were more active in proliferation in vitro, increased in number in human keloid and normal tissues, as compared with CD26− population (Xin et al. 2017). Also, CD26+ fibroblasts more actively release cytokines, collagens, and extracellular matrix (ECM) elements. CD26/DPP4 is recognized to be superior as a marker of murine dermal fibroblasts to other fibroblast markers such as CD73, CD90, biglycan, and prolyl-4-hydroxylase beta (Rinkevich et al. 2015), although it has been described as specific for the upper (papillary) dermis during fetal development of mice (Driskell et al. 2013). In accordance with this, we can confirm this staining tendency in the skin of adult normal mice (Fig. 1). The inhibition of CD26/DPP4 reduces cutaneous scar formation during wound healing (Rinkevich et al. 2015). Although the rate of healing was decreased in inhibitor-treated animals as compared with controls, final scar formation in treated wounds was reduced in size (Rinkevich et al. 2015). The expression of CD26/DPP4 and number of CD26/DPP4-expressing fibroblasts upregulated in the skin of systemic sclerosis patients, and loss of CD26/DPP4 activity by gene knockout or treatment with DPP4 inhibitors diminished dermal or pulmonary fibrosis (Soare et al. 2020).

Although the subcellular localization of CD26/DPP4 in fibroblasts has not been investigated in detail, electron microscopic observation has reported its localization in fibroblast-like synoviocytes from human arthritis; CD26/DPP4 together with aminopeptidase N/CD13 are localized in membrane domains associated with caveolae (Riemann et al. 2001). In contrast, some fibroblasts in the rat salivary gland display a diffuse immunoreactivity in the cytoplasm under electron microscopy (Sahara and Suzuki 1984). Even at a light microscopic level, the whole cytoplasm of dermal fibroblasts appears to be immunolabeled by a CD26/DPP4 antibody (Fig. 1).

**Exocrine glands and endocrine glands**

Salivary glands have attracted research interest due to the rich and rigorous expression of CD26/DPP4 within secretory portions. Gosssau (1979, 1981), using enzyme histochemistry, demonstrated a predominant localization of CD26/DPP4 in the secretory granules of acinar cells in the submandibular and parotid glands. In contrast, Sahara and colleagues localized CD26/DPP4 mainly on the plasma membranes of acinar cells, intercalated ducts, and striated duct cells, but not within the secretory granules of acinar cells (Fukasawa et al. 1981a, b). Electron microscopically, an antiserum against CD26/DPP4 labeled the luminal plasma membranes of acinar cells and intercalated and striated ducts in the rat salivary glands (Sahara and Suzuki 1984). Another immunoreactivity was found in the plasma membrane of intercellular canaliculi continuous to the glandular lumen. The subcellular localization agrees with the general consensus regarding CD26/DPP4, namely, that it is a membrane-bound peptidase. By using CD26/DPP4 as a marker of the luminal membrane, Sahara (1985) visualized tubular invaginations of the luminal membrane and subsequent fusing to secretory granules located more internally in the parotid acinar cells of rats. Al-

![Fig. 1](image-url)
though the functional significance of CD26/DPP4 in salivary secretions remains unknown, CD26/DPP4 with a proteolytic activity against substance P and GIP is found in human saliva and released via exosome-like vesicles (Ogawa et al. 2008). Thus, it is possible that the released CD26/DPP4 can modify bioactive substances. Overexpressed DPP4/CD26 in the saliva of primary Sjögren’s syndrome patients has been noted and is related to immunological dysfunction since cytokines and chemokines are also the main substrates for this enzyme (Garreto et al. 2021).

Our immunohistochemical analysis using an anti-CD26 antibody in the mouse salivary glands demonstrated its intense and consistent localization throughout the luminal side of acini, the intercalated duct, striated duct, and intra- and interlobular ducts of various sizes (Fig. 2), in agreement with Sahara and Suzuki (1984) and Sahara (1985). Contents in the lumen of the excretory system appeared to be heavily immunolabeled with the same antibody. Weak but significant expression of CD26/DPP4 is present along the basolateral membrane of acinar cells. A part of secretory granules close to the lumen of acini are immunoreactive for CD26 even by light microscopy, in partial accordance with observations by Sahara (1985). Furthermore, CD26/DPP4 has been demonstrated in secretory granules of the parotid gland and submandibular gland (Gossrau et al. 1981) as well as endocrine cells such as pancreatic glucagon cells (Poulsen et al. 1993; Grondin et al. 1999). This phenomenon suggests two possibilities: (1) authentic localization of CD26 within some secretory granules and on granule membrane before exocytosis, or (2) invagination of the luminal membrane to fuse secretory granules during rapid secretion. The granular localization of the membrane-anchored proteinase may be supported by another example of membranous protein associated with secretory granules.

GP2, a glycoprotein with a molecular weight of 75–92,000, was originally identified as the major protein in zymogen granules of pancreatic acinar cells. GP2 is bound to the limiting membrane of secretory granules, targeted to the apical plasma membrane, and mostly released into pancreatic secretions (Fukuoka et al. 1991, 1992; Scheele et al. 1994). Like GP2, CD26/DPP4 may be released into saliva and process bioactive substances such as substance P and GIP, cytokines such as SDF-1 and RANTES, and growth factors such as EGF and NGF, abundant in saliva (Ogawa et al. 2008).

In endocrine glands, the enzyme activity of CD26/DPP4 in rats differs among organs (Sahara et al. 1981b); the adrenal gland displayed the highest activity, followed by the pancreas and thyroid gland. Immunohistochemically, vascular endothelial cells of endocrine glands, which are sinusoidal capillaries in type, were intensely immunolabeled in the adrenal cortex, thyroid, and parathyroid gland, whereas the immunoreaction was considerably faint in the pituitary gland, pineal gland, and pancreatic islets (Sahara et al. 1981b).

Liver
In the liver, CD26/DPP4 activity, as demonstrated by both enzyme histochemistry and immunohistochemistry, is high in the entire biliary tree including interlobular bile ducts and other bile ducts with large diameters. The most impressive images for the ubiquitous localization of hepatic CD26/DPP4 is seen in bile canaliculi up to the end portion, indicating a powerful cell marker of bile canaliculi in addition to classical markers, such as alkaline phosphatase and several ATPases. The predominant localization in the bile canaliculi was not zonated from periportal to centrolobular areas in the hepatic lobules (rat: McCaughan et al. 1990; Fukui et al. 1990; Tarantola et al. 2012). In contrast, Matsumoto et al. (1992) recognized a clear zonation in normal human liver with intense staining of bile canaliculi in zone 3 and faint reactivity in periportal zone 1. Another positive immunoreactivity was seen in sinusoidal lining cells of the mouse liver (Mentzel et al. 1996), namely the endothelium of the “discontinuous” type with various sizes of pores and gaps.
involvement of CD26/DPP4 in binding, absorption, and modification of secreted proteins, although it remains unclear what substances are the target of this enzyme.

Pancreas

Cellular localization of CD26/DPP4 differs according to mammalian species, preparation procedure (fixation and types of sectioning), and staining methods. The endocrine pancreas is representative of such organs (Table 1). In the human pancreas, islets — especially glucagon cells — and ductal cells — intercalated ducts and intra- and interlobular ducts — express CD26/DPP4, but not exocrine acini.

![Fig. 3](image)

CD26/DPP4 immunoreactivity in the mouse liver. 

(a) Double immunostaining for CD26/DPP4 and LYVE-1. CD26/DPP4 is found in bile canaliculi (green), while sinusoidal endothelium is labeled red with antibody against LYVE-1. 

(b) A higher magnified picture shows an intense expression of CD26/DPP4 in sinusoidal endothelium as well as bile canaliculi. However, the immunoreactivity decreases in intensity in the central vein indicated by an asterisk.

| Table 1 Immunoreactivities of CD26/DPP4 in the pancreas, especially pancreatic islets |
|---|
| species | sections | cell types | authors |
| human | frozen/paraffin section | duct cells | Dinjens et al. 1989 |
| human | frozen section | insulin cells, ducts | Augstein et al. 2015 |
| human | frozen section | glucagon cells, ducts | Busek et al. 2015 |
| human | paraffin section | insulin cells | Rahman et al. 2015 |
| human | paraffin section | glucagon cells | Omar et al. 2014 |
| mouse | frozen section | insulin cells, ducts | Mentzel et al. 1996 |
| mouse | paraffin section | insulin cells | Omar et al. 2014 |
| mouse | frozen section | duct cells | our study |
| rat | frozen section | exocrine portion/ducts | Sahara et al. 1981b |
| rat | frozen section | intercalated ducts/acinar cells | Hartel et al. 1988 |
| rat | frozen section | duct cells | McCaughan et al. 1990 |
| mouse/rat | paraffin section | glucagon cells | Liu et al. 2014 |
| human/pig | paraffin section | insulin cells | Liu et al. 2014 |
| pig | paraffin section | glucagon cells | Poulsen et al. 1993 |
| pig | resin section | glucagon cells | Grondin et al. 1999 |

(Fig. 3). The sinusoidal endothelium is known to possess various receptors for plasma proteins, hormones, and ECM-derived substances including collagen and chondroitin sulfate. Due to the active uptake activity, sinusoidal endothelial cells are considered scavenger endothelial cells (Sørensen et al. 2012). CD26/DPP4 may function as one of these receptors for the uptake and degrading of circulating substances.

The salivary glands and liver have a common localization of CD26/DPP4 in exocrine glands, namely, in the excretory system beginning at the lumen of acinus/intercellular canaliculi continuing until ducts with large diameters. This image suggests the involvement of CD26/DPP4 in binding, absorption, and modification of secreted proteins, although it remains unclear what substances are the target of this enzyme.
Localization of CD26/DPP4 in the islets, predominantly in insulin cells (Rahman et al. 2015). In murine pancreas, CD26/DPP4 was expressed predominantly in insulin cells, whereas in the human and pig pancreas glucagon-secreting alpha cells exclusively expressed CD26/DPP4 (Poulsen et al. 1993; Grondin et al. 1999; Liu et al. 2014; Omar et al. 2014). These inconsistent findings for cellular localization can most likely be ascribed to the type of sections — paraffin sections vs. frozen sections. On the other hand, it should be noted that glucagon cells among gut hormone-secreting cells tend to induce non-specific bindings caused by ionic binding mechanisms (Grube and Aebert 1981).

A few studies have dealt with the cellular distribution of CD26/DPP4 in the exocrine pancreas as compared to the endocrine pancreas. The human exocrine pancreas displayed positive immunostaining in luminal membranes of intra- and inter-lobular pancreatic ducts but not in islets or exocrine acini (Dinjens et al. 1989b). In the rat pancreas, the exocrine portion demonstrates an intense immunoreaction, where only the luminal surface of the excretory duct is reported to be immunolabeled (Sahara et al. 1981b). Our immunostaining of the mouse pancreas demonstrated a predominant localization in the duct systems, where primary cilia, sensors of pancreatic fluid, are also immunolabeled (Fig. 4).

Intestine and lung
This enzyme was originally purified from several organs including the kidney and small intestine, where it occurs in high amounts in the brush border of the proximal tubules and enterocytes, respectively. The brush border staining of CD26/DPP4 has been documented in the small and/or large intestine of rats (Dinjens et al. 1989a; McGaughan et al. 1990), mice (Mentzel et al. 1996), pigs (Poulsen et al. 1993), and humans (Hansen et al. 1999). CD26/DPP4 exists in intestinal juice obtained from the Sunda pangolin, insect-eating mammals (Zhang et al. 2019), although it is unknown whether the enzyme originates from the intestine or pancreas. An in vitro study using human intestinal cell lines reported that intestinal epithelial cells secreted exosome-like vesicles containing CD26/DPP4 (van Niel et al. 2001).

In the human and murine lungs, alveolar epithelial cells (type I and type II cells) displayed membrane-associated immunoreactivity for CD26/DPP4 (Dinjens et al. 1989b; Mentzel et al. 1996). In contrast, capillary endothelia of alveoli have been visualized in the rat lung using monoclonal antibodies that are directed against CD26/DPP4 contained in endothelial cell surface molecules (Johnson et al. 1993).

Kidney and urine
Analyses of DPP4 activity using Gly-Pro-pNA as a substrate demonstrated the highest activity in the rat kidney, being almost 6 times higher than that of the lung or spleen, with the second highest activity (Hildebrandt et al. 1991; Wang et al. 2014). In the rat, the predominant immunoreaction was localized in the brush border of proximal tubules (Fukasawa et al. 1981; Hartel et al. 1988; Wang et al. 2014). Renal glomeruli as well as the proximal tubular epithelium were heavily immunolabeled in rats (sexes unknown) (McCaughan et al. 1990), although immunostaining of glomeruli and brush border of proximal tubules in rats displayed distinct sex difference between the two portions (Hartel et al. 1988). Electron microscopically, CD26/DPP4 is localized in the apical plasma membrane covering the brush border in the proximal tubules of mice (Mentzel et al. 1996) and rabbits (Girardi et al. 2001). The luminal cell membrane of both the glomerular endothelium and the apical cell membrane of podocytes which faces the urinary spaces (Bowman spaces) expressed CD26/DPP4 under electron microscopy (Dekan et al. 1990), being in agreement with heavy immunolabeling and enzyme-histochemical activity in the whole glomeruli. In the murine glomeruli, CD26/DPP4 is located on the cell membrane of...
podocytes but not on the endothelial or mesangial cells (Mentzel et al. 1996). Another expression in the renal medulla is characterized by the vasa recta running parallel to Henle’s loop and collecting tubules. Interestingly, many studies by DPP4 inhibition in non-human studies revealed a reduction in proteinuria/kidney injury independent from glucose lowering (Nistala and Savin 2017).

CD26/DPP4 is present in urine and found in extracellular vesicles (exosomes) collected from human urine (Liu et al. 2018). Tamm-Horsfall protein (THP) is a GPI-anchored membrane protein produced in the kidney. THP in the urinary tubules is intracellularly present in membrane-bound clear vesicles in the apical cytoplasm (Bachmann et al. 1985) and also distributed along the entire plasma membrane of epithelial cells in the thick ascending limb of the loop of Henle (Hoyer et al. 1979), suggesting the release of THP into urine. In fact, THP is a predominant glycoprotein present in mammalian urine and possesses an ability to trap pathological bacteria (Kokot and Dulawa 2000).

Blood vessels
Vascular endothelia in many organs express CD26/DPP4, which may be partially released into blood circulation. The half-life of peptide hormones including GLP-1 is less than 2 min owing to DPP4 activity in blood. Sinus endothelia in the liver, adrenal medulla, and spleen showed more intense immunoreactivity than capillary and arterial endothelia (Hartel et al. 1988), possibly giving a clue when considering the roles of sinusoidal CD26/DPP4 as mentioned below. Capillary endothelia were also immunoreactive for CD26/DPP4 in various organs, including the lung, pancreas, and medullary region of the kidney (Hartel et al. 1988). Immunoreactivity for CD26/DPP4 in human intestine is seen in capillaries in all layers of the intestinal wall as well as the brush border of enterocytes (Hansen et al. 1999). In the mouse lung, type I alveolar cells but not capillary endothelial cells are reported to possess immunoreactivity for CD26/DPP4 (Mentzel et al. 1996). However, according to Johnson et al. (1993), several monoclonal antibodies recognizing CD26/DPP4 intensely stained the endothelium of pulmonary capillaries but not those of other types of blood vessels of large caliber. In an investigation using the same antibodies, the endothelium of other organs was found to be largely lacking in positive staining except for the splenic sinuses, the vasa recta of the kidney medulla, the brush borders of urinary tubules, and bile canaliculi of the liver (Johnson et al. 1993). Positive staining in sinuses of the spleen is consistent among researchers (McCaughan et al. 1990). Interestingly, the splenic sinus endothelium plays an important role in the selection and filtration of aged erythrocytes to remove them from circulation. Vascular endothelial cells express CD26/DPP4 in muscular tissues of the skeletal muscle and heart (McCaughan et al. 1990) but not in the brain (Mentzel et al. 1996); the mouse brain displayed positive immunostaining in astrocytes.

CD26/DPP4 was identified as an endothelial cell surface antigen which is selectively recognized by circulating cancer cells during metastasis (Johnson et al. 1993). Johnson et al. suggested that CD26/DPP4, a fibronectin-binding protein, is involved in the vascular adhesion and metastasis of cancer cells, since fibronectin is bounded and expressed on cancer cell surfaces. Also in earlier works, its intimate relation with the collagen metabolism has been suggested, including cell spreading on the extracellular matrix, due to the high content of Gly-Pro sequences in collagen (Hanski et al. 1985, 1986).

Immune system, thymus, and lymph node
CD26/DPP4 participates in the differentiation and activation of lymphocytes, thereby being identified as a T cell activation protein. Especially, CD26/DPP4 contributes to T cell maturation/homeostasis and antigen-presenting cell interaction to T cells, having a significant role in many autoimmune and inflammatory conditions (Zhao, 2019). Graft-versus-host disease (GVHD) is initiated by antigen-presenting cells such as interdigitating cells and macrophages and following the activation of donor-derived T cells. Expression of CD26/DPP4 is upregulated on activated lymphocytes, possibly in response to cytokines. Antigen stimulation increased the percentage of CD26+CD4+ cells and CD26+CD8+ T cells, and DPP4 inhibitors suppressed the proliferation of CD4+ and CD8+ T cells. CD26/DPP4 activity in serum and synovial fluid decreased in patients with rheumatoid arthritis, a chronic autoimmune disease, while anti-CD26 antibodies increased in rheumatoid arthritis, suggesting that the anti-CD26 levels in the serum are useful as a diagnostic indicator (Zhao, 2019).

Histochromically, lymphocytes of thymus and T cell areas in the lymph node and spleen are immunolabeled for CD26/DPP4 (McCaughan et al. 1990; Gorrell et al. 1991; Mentzel et al. 1996). In accordance, thymocytes express CD26/DPP4 on the cell surface, with higher expression in the cortex of the mouse thymus, as confirmed under electron microscopy (Mentzel et al. 1996). According to immunos-
Localization of CD26/DPP4

CD26 was recognized in more than 80% of lymphocytes in the lymph node and more than 78% of splenocytes in the rat. CD26/DPP4 is detected in natural killer cells and macrophages, where cytoplasmic granules/lysosomes are possibly a subcellular site for storage.

Possible functions and clinical aspects

The exact functions of CD26/DPP4 remain unsettled or heterogeneous, as suggested by its broad distribution. One of the predominant functions is the inactivation of circulating hormones, such as incretins. The degradation of bioactive peptides occurs once the peptides enter the systemic circulation. Representative sites exerting this activity are believed to be the liver and kidney, where CD26/DPP4 is present as a membrane-bounded ectoenzyme exposed to the bloodstream or renal infiltrate. On the other hand, Hansen et al. (1999) proposed that GLP-1 is sufficiently degraded by DPP4 on the local capillary endothelium before entering the portal and following general circulation.

Cell surface localization of CD26/DPP4 in the intestine, kidney, and endothelium suggests the movement of CD26/DPP4 from the plasma membrane to intracellular vesicles during endocytotic processes. The mechanism of internalization may be explained by existence of rafts, namely glycolipid- and cholesterol-rich special microdomains, rather than coated pits and vesicles (Riemann et al. 2001; Mentlein 2004). Degradation also occurs in some degree within the bloodstream, where CD26/DPP4 is present in a soluble form. The soluble, truncated form of DPP4 (sCD26), occurs in other body fluids as well as serum. Since lymphocytes and other myeloid cells express this enzyme, the bone marrow is recognized as the predominant source of serum CD26/DPP4 (Wang et al. 2014). The soluble forms have no transmembrane domains in lacking the first 30–40 amino acids and are thought to shed from the membrane or be released by the use of exosomes into plasma; however, it maintains its enzymatic activity.

The regulation of cellular and extracellular matrix interactions has attracted the attention of researchers. CD26/DPP4 affects the invasiveness of many cancer cells; accumulating evidence suggests the binding of CD26/DPP4 to collagen and fibronectin. The expression profile in tumor cells and the binding ability may confer an aggressive or metastatic phenotype onto tumor cells. Involvement of CD26 in cancers is characterized by two clinical aspects: use of a serum diagnostic marker and an understanding of the mechanisms for invasion/metastasis. As a serum diagnostic marker, CD26/DPP4 has been identified for colorectal cancer (Cordero et al. 2000; 2011) and gastric cancer (Boccardi et al. 2015). Serum CD26/DPP4 levels are increased in patients with hepatic cancer and in rats with experimental hepatic cancer (Kojima et al. 1987; Nishina et al. 2019), while being decreased in many cancers including colorectal cancer (Cordero et al. 2000, 2011) and gastric cancer (Boccardi et al. 2015) or silenced in melanoma (Wesley et al. 1999). CD26/DPP4 is expressed on melanocytes as well as epithelia, fibroblasts, and T cells, and a loss of CD26/DPP4 expression occurs during melanoma progression. Thus, re-expressing CD26/DPP4 in melanoma cells induces phenotypic changes into normal melanocytes (Wesley et al. 1999). The inconsistent expression in various cancer patients may be explained by the finding that serum CD26/DPP4 is partially derived from activated T cells. Upregulation or downregulation of the ectopeptidase in cancers appears to be specific to tissues/cells, stages, and malignancies.

The population of CD26 fibroblasts with an enhanced activity of collagen production is selectively increased during wound healing (Worthen et al. 2020). Treatment with Sitagliptin, a DPP4 inhibitor, diminished CD26 expression to impair the collagen synthesis of fibroblasts as well as their proliferation and migration (Jiang et al. 2021).

Subcellular localization is important when considering the function of CD26/DPP4. The most predominant localization is associated with apical and luminal plasma membranes, although such information other than for membrane localization is scanty. We should pay attention to its cytosolic intracellular localization rather than membrane-bound existence when we discuss functions and dynamics. For example, intracellular immunolabeling with a granular appearance was documented on bone marrow smear preparations of rats (Wang et al. 2014). Also, the existence in lysosomes and multivesicular bodies suggests intracellular degradation and release via exosomes.

In conclusion, predominant localization sites of CD26/DPP4 include the luminal surface of excretory organs, brush border of epithelia, vascular endothelia, fibroblasts, T cells and other myeloid cells. Its expression in the pancreas including islets, which is important when considering the mechanism of DPP4, is inconsistent among researchers. Since CD26/DPP4 is implicated in the regulation of the cell-matrix adhesion, the increasing importance of
this enzyme is recognized in studies in the fields of inflammation, immune disease, and tumorigenesis. Knowledge of the existence and disease-dependent changes of soluble CD26/DPP4 in body fluids is essential for clinical diagnosis and treatment.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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