

# Development of the dipeptidyl peptidase 4 family and its association with lung diseases: a narrative review

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**Background and Objective:** Dipeptidyl peptidase (DPP)4 is a member of a subfamily of serine peptidase S9. DPP4, expressed as a type II transmembrane protein, has a wide tissue distribution and is most active in the lung and small intestine. Many substrates of DPP4 have been identified, including neuropeptides, chemokines, and glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptides (GIPs). DPP4 inhibitors are clinically useful in the treatment of type 2 diabetes mellitus. DPP9, an N-terminal dipeptide targeting enzyme with proline or alanine, may have DPP4-like activity. DPP9 is ubiquitously expressed at human and rodent messenger RNA (mRNA) levels and therefore may play a role in the immune system and epithelial cells. It has been shown that DPP9 plays an important signaling role in the regulation of survival and proliferation pathways and is also involved in cell migration, apoptosis, and cell adhesion. In recent years, there has been further progress in DPP9 inhibition through activation of apoptosis by the inflammasome sensor protein Nlrp1b. This study aims to investigate the association of DPP4 family members and DPP9 with lung disease.

**Methods:** The literature search was initiated using the PubMed database. We searched for the content (DPP4) AND (Lung Diseases), (DPP9) AND (Lung Diseases), from which we filtered the literature we needed.

**Key Content and Findings:** Given the high biological activity of the DPP4 family, their involvement in various lung diseases is highly relevant. There is growing evidence for the importance of DPP4 and DPP9 of the DPP4 family in lung diseases, which are closely associated with diseases such as asthma, lung infections, pulmonary fibrosis (PF), and lung cancer.

**Conclusions:** This review summarizes most of the current evidence that DPP4/9 is associated with lung disease. Within the DPP4 family, the role of DPP4 in particular in respiratory disease is important.

Keywords: Dipeptidyl peptidase 4/9 (DPP4/9); asthma; pulmonary infections; lung cancer

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# Introduction

Dipeptidyl peptidase (DPP), an endogenous membrane glycoprotein and serine extrapeptidase, cleaves the X-proline dipeptide from the N-terminus of the polypeptide. It is an antigen expressed on the surface of most cell types and is associated with immune regulation, signal transduction, and apoptosis. The substrates of DPPs are prolinecontaining peptides, including growth factors, chemokines, neuropeptides, and vasoactive peptides. DPP4 is a member of a subfamily (also known as the 'DPP4 Gene Family') of the serine peptidase family S9, which includes DPP4 and DPP9 (1). DPP4 is a cell-surface transmembrane glycoprotein originally described in 1966 of having DPP activity. DPP4 has multiple bioactive substrates and is involved in multiple pathophysiological processes. The close association of the DPP4 family with diseases such as asthma and lung infections has led to widespread interest in the DPP4 family. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1158/rc).

# Methods

The literature search was initiated using the PubMed database, which is sourced from MEDLINE and has a core theme of medicine. We searched for the content (DPP4) AND (Lung Diseases), (DPP9) AND (Lung Diseases), from which we filtered the literature we needed (*Table 1*).

# Key content and findings

# **DPP4** overview

DPP4 [also known as adenosine deaminase (ADA)-binding protein or CD26] is an N-terminal dipeptide targeting enzyme with proline, which is present in soluble and membrane-bound form (2) (*Figure 1*). A soluble form of sCD26/DPP4 can be found in body fluids (3). It is distributed extensively in mammalian tissues as an integral plasma membrane protein (4). DPP4 activity is highest in the lung and small intestine and moderate in tissues such as the pancreas, liver, and kidney (2). The expression of DPP4 activity depends on cell fusion in different epithelial cell lines (5). The widespread distribution of DPP4 on the lung parenchyma, epithelium, vascular endothelium, and human bronchopulmonary fibroblasts suggests that DPP4 may play an important role in regulating lung physiology and pathology. This dipeptidase has a variety of substrates, including cytokines, growth factors, neuropeptides, and enterokinetic hormones that are either activated, inactivated, or modulated with respect to receptor specificity by CD26/DPP4-mediated cleavage (6). This includes glucagon-like peptide-1 (GLP-1), and both DPP4 and GLP-1 have roles in intracellular signaling, oxidative stress, lipid metabolism, apoptosis, immune activation, insulin resistance and inflammation (7). It also plays an important role in regulating glucose homeostasis and the metabolism of the incretin hormones GLP-1 and gastric inhibitory polypeptide (GIP). In 2022, Brabenec et al. have shown that calcitoningen acts on the vascular endothelium to protect endothelial barrier integrity and is a major effector of the beneficial effects of DPP4 inhibitors and has a direct impact on vascular integrity (8). DPP4 activity is known to be regulated at many levels, including control of gene and protein expression, interaction with substrates, and regulation of enzyme activity (9,10).

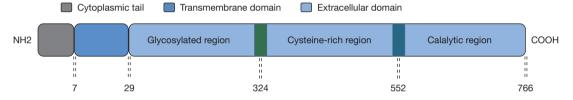
# Association with chronic obstructive pulmonary disease (COPD)

COPD is a multifactorial disease of the respiratory system characterized by chronic airflow impairment and increased airway inflammation. Complications are common in patients with COPD and may significantly affect their quality of life, symptom severity, and the eventual outcome (11,12). It has become an important public health problem and will remain a challenge for clinicians in the 21st century, as its high morbidity, morbidity, and mortality rates pose major challenges to the health-care system (13). In 2018, Seys et al. proposed a protective role for miRNA-218-5p (miR-218-5p) in cigarette smoking-induced inflammation and COPD (14). And then they found that DPP4 messenger RNA (mRNA) and protein levels were higher in patients with smoking and COPD, and that the increase in DPP4 was mainly located in alveolar epithelial cells rather than bronchial and bronchiolar epithelial cells. In addition, DPP4 levels also correlated with COPD stage and smoking status (15).

The pathology of COPD has not been fully elucidated, but the dysregulated chronic immune response is thought to be an important driver (16). Furthermore, their study investigated the effect of protease DPP4 on tissue remodeling in lung tissue samples from patients with COPD. Activated alveolar macrophages showed a strong positive staining for DPP4. DPP4 was significantly upregulated in type I and type II alveolar epithelial cells. The authors also noted an association between mesenchymal

Items	Specification
Date of search	2022.10.01
Databases searched	PubMed
Search terms used	(DPP4) AND (Lung Diseases)
	(DPP9) AND (Lung Diseases)
Timeframe	1990–2022
Inclusion and exclusion criteria	Inclusion: mainly in English; DPP4/9 articles related to respiratory diseases, including COPD asthma, pneumonia, lung cancer, PF, tuberculosis, and PH
	Exclusion: thoracic surgery-type diseases, no restrictions on article types
Selection process	Primarily selected for DPP4/9 association with lung disease, independently performed

 Table 1 The search strategy summary



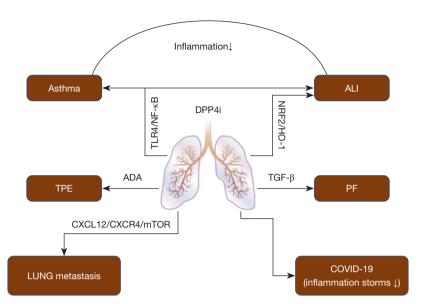
**Figure 1** The principal structure of DPP4 consists of the cytoplasmic tail (1–6 amino acids), the transmembrane domain (7–29 amino acids), and the extracellular domain (30–766 amino acids). DPP, dipeptidyl peptidase.

cell hypertrophy and increased DPP4 staining (17). The remodeling response to COPD also revealed a rapid turnover of extracellular matrix proteins, a change that was increased during the exacerbation (18). Proteases are known to be critical for chemokine activation, and DPP4/ CD26 also acts on CXCL12. Thus, protease activity may directly or through chemokine modulation exacerbate tissue degradation in COPD.

# Association with asthma

Asthma is a chronic inflammatory disease caused by incompletely understood heterogeneous gene-environment interactions. They are characterized by airway obstruction and bronchial hyperreactivity. Clinically, patients with asthma present with recurrent episodes of wheezing, cough, chest tightness, and shortness of breath. The immunopathobiology of asthma is complex and involves many cellular interactions with different effects (19). CD26 has been reported to be involved in asthma and airway inflammation (20). It is well known that T-lymphocyte numbers play an important role in the pathogenesis of asthma. The main finding in this study is that decreased

CD4 T-cell numbers in CD26-deficient F344 rats suggests a decreased inflammatory state. This is the first demonstration that CD26 is directly associated with T-cell recruitment and immunoglobulin E (IgE) production in a model of airway inflammation. The use of CD26 inhibitors may be a new approach to treating asthma and airway inflammation (21). DPP4 functions as adhesion receptor for collagen and fibronectin proteins involved in epithelial repair in epithelial cells (22). In their study, Schade et al. (23) demonstrated increased DPP4 activity in bronchoalveolar lavage fluid and lung parenchyma in an experimental rat model of asthma, predominantly in the bronchial epithelium of the airway. Yan et al. (24) suggested in their study that in the pathogenesis of allergic asthma, leukocyte infiltration, especially eosinophils, was significantly increased in the lungs of CD26 knockout mice, suggesting that CD26 is required to control eosinophil-mediated airway inflammation. Analysis of the effects of different doses of the competitive DPP4 inhibitor isoleucine at different time points using different routes of administration has shown that local suppression of DPP4 is beneficial for allergic symptoms and that sustained suppression exacerbates



**Figure 2** The role of DPP4 inhibitors in lung diseases, such as asthma where they reduce airway inflammation. DPP4 inhibition attenuates TLR4/NF- $\kappa$ B pathway-mediated inflammation and NRF2/HO-1 pathway-mediated oxidative stress. It alleviates the inflammatory storms of COVID-19 and PF, etc.  $\downarrow$ , decrease. ALI, acute lung injury; DPP, dipeptidyl peptidase; ADA, adenosine deaminase; TPE, tuberculous pleural effusion; TGF- $\beta$ , transforming growth factor- $\beta$ ; PF, pulmonary fibrosis; LUNG, lung cancer; COVID-19, coronavirus disease 2019.

the allergic-induced inflammatory process (25). CD26 is part of the homeostatic mechanism that downregulates T helper (Th)2-mediated airway inflammation (26). It has been suggested that DPP4 is highly expressed in human asthmatic bronchial epithelial cells and is induced by IL-13 and promotes fibronectin production (27). In the past 2 years, the DPP4 inhibitor, saxagliptin, has been reported to reduce airway inflammation and protect against ovalbumin-induced allergic asthma by regulating TLR4 and NF- $\kappa$ B and by enhancing antioxidant activity (28) (Figure 2). It has also been reported that sitagliptin, another DPP4 inhibitor, plays an important role in ameliorating inflammation and remodeling in a mouse model of chronic asthma (29). Together, these data suggest that DPP4 is involved in asthma and airway inflammation through modulation of cell adhesion and T cell activation and affects immune responses, and that inhibition of DPP4 may be a new treatment for airway inflammation.

# Association with lung infections

Bacteria and viruses are the major causes of lung infections and complications, and the incidence and mortality of these infections are increasing each year in populations, particularly in the elderly, infants, and individuals with hereditary diseases, but the underlying mechanisms determining the increased susceptibility to lung infections have not been fully established (30). Acute lung injury is the injury of alveolar epithelial cells and capillary endothelial cells by various direct and indirect causative factors, resulting in diffuse pulmonary stroma and alveolar edema, reduced lung volume, decreased pulmonary compliance, and imbalanced ventilation/flow ratio as pathophysiological features, clinically manifested as progressive hypoxemia and respiratory distress (31). In their study, Guo et al. suggested the DPP4 inhibitor saxagliptin reduced lipopolysaccharide (LPS)-induced oxidative stress, inflammation, and apoptosis in patients with acute lung injury by modulating the NRF2/ HO-1 and NF-KB pathways, supporting the evidence for the use of inhibitors in the treatment of acute lung injury (32). Zhou et al. showed that LPS stimulation activated TLR4/ NF-KB signaling and induced oxidative stress, and that the DPP4 inhibitor, tragliptin, may attenuate inflammation and oxidative stress in LPS-induced acute lung injury mice (33).

The Middle East respiratory syndrome (MERS) that emerged in the previous years belongs to the Coronaviridae family of RNA viruses. Lu *et al.* (34) suggested in their study that CD26 was identified as a cellular receptor for the MERS.CD26 is the third peptidase identified as a functional coronavirus receptor. The recognition of CD26 by the MERS is mediated by the viral surface protruding proteins. Ohnuma *et al.* showed in the literature that CD26 may be a suitable target for the treatment of this disease (35). A novel MERS-like coronavirus transmitted in Malayan pangolins, named Manis javanica HKU4-related coronavirus (MjHKU4r-CoV), has recently been reported in the literature. The virus utilizes human DPP4 (hDPP4) as a receptor and host protease for cellular infection. MjHKU4r-CoV-1 is infectious and pathogenic in the human respiratory tract as well as in hdpp4 transgenic mice (36).

Coronavirus disease 2019 (COVID-19) is a pandemic disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) that threatens the health of people worldwide and it is highly contagious. The disease ranges from asymptomatic or mild symptoms to severe pneumonia and acute respiratory distress syndrome. Asthma and other allergies have not been identified as major risk factors for COVID-19 because the number of asthmatic patients infected is not high enough to account for this factor. The occurrence of COVID-19 in patients with COPD may be related to smoking. Cancer patients are usually more vulnerable to infections, including lung cancer. There is currently no clear treatment for COVID-19 (37). Zhang et al. (38) in their study pointed out that during the global epidemic of COVID-19, DPP4 was found to be an important marker that may play an important role in disease progression. Nafakhi et al. (39) proposed in their study that DPP4 inhibitors might have a potentially beneficial effect in the treatment of COVID-19. DPP4 inhibitor such as glial protein has been reported to significantly reduce viral infection and reproducibility and decrease lower airway cytokine storms and inflammation in patients with COVID-19 (40,41). Posadas-Sánchez et al. showed that the presence and severity of COVID-19 correlated with lower levels of DPP4, which was more susceptible to infection and disease progression (42).

#### Association with tuberculous pleurisy

Tuberculous pleural effusion (TPE) is considered a form of extrapulmonary tuberculosis, and measurement of thymic ADA levels may be helpful in the diagnosis. Oshikawa *et al.* (43) study found a significant increase in soluble CD26 in pleural effusions from patients with tuberculous pleurisy, and elevated soluble CD26 was associated with Th1-like immune responses and may be a useful marker of tuberculous pleurisy. It has also been reported in the literature that the enzyme DPP4 is closely related to the enzyme ADA, whereas both ADA and DPP4 play an important role in the pathogenesis of tuberculous immunity, and that measurements of ADA and DPP4 are helpful in the diagnosis of TPE with higher specificity, sensitivity, and effectiveness (44). Wang *et al.* (45) noted in the literature that the combination of ADA and DPP4 promoted the differentiation of TPE and non-TPE, improved specificity and diagnostic efficiency, and the measurements improved the diagnostic value of pleural effusion in tuberculosis. However, it has also been reported that DPP4 may enhance the specificity of the pulmonary tuberculosis detection assay with ADA, but does not improve the sensitivity (46).

Association with lung cancer and pulmonary metastases Lung cancer is the leading cause of death among men and women worldwide, accounting for approximately 1.6 million deaths per year, a 5-year overall survival rate of only 15%, and most cases of lung cancer being detected late. The distinction between intrapulmonary metastases and newly diagnosed primary carcinomas may be difficult, especially when the histology is similar (47). It has been previously reported that the molecular properties of DPP4 may differ between normal and cancerous lung tissues (48). Squamous-cell lung cancer showed a significant increase in the specific activity of the DPP4 enzyme and a significant correlation in the tumor/lung activity ratio (49). Subsequent literature suggested that DPP4 may be a good marker for differentiating adenocarcinoma from other histologic types of lung cancer (50). Cheng et al. reported that DPP4 is an endothelial cell adhesion molecule in rat breast cancer cells and mediates pulmonary vascular arrest and metastasis in these cells (51,52). Subsequently, They showed that decreased expression of DPP4 in the pulmonary capillary endothelium of Fischer 344/CRJ rats significantly affected lung colonization of breast cancer cells (53). In 2010, Lin et al. (54) found that in the absence of DPP4, elevated IGF-1 levels may contribute to early carcinogenesis in squamous cell carcinoma of the lung. Yang et al. (55) reported in the literature that DPP4 inhibition accelerates epithelialmesenchymal transition (EMT) via the CXCL12/CXCR4/ mTOR axis, thereby accelerating breast cancer metastasis to the lung. Recent advances in anticancer research have shown that aminoguarin derivatives have strong anticancer activity as DPP4 inhibitors, particularly against A549 cell lines, as demonstrated by the study of Soni and Soman (56). Wang et al. (57) found in a recent study that compound 6c is a potent inhibitor of DPP4, which can be detected in a variety of tissues and is most abundant in the lung, suggesting an impact on lung cancer or other respiratory diseases. Factor DPP4 plays a complex role in different histologic types of lung cancer through interactions with other key molecules and immune regulation.

#### Association with pulmonary fibrosis (PF)

PF is caused by a variety of lung injuries, including toxic, autoimmune, pharmacologic, infectious, or traumatic lesions, mainly manifested as pulmonary inflammation, persistent alveolar injury, and excessive extracellular matrix accumulation (58). Idiopathic PF (IPF) is a chronic progressive respiratory disease characterized by terminal respiratory failure. Irreversible lung injury and limited treatment options result in high mortality with 5-year survival of only 20%. Fibroblasts are key effector cells in fibrotic disease, whereas DPP4 is a marker of activated fibroblasts, and transforming growth factor- $\beta$  (TGF- $\beta$ ) is the core pathway for fibrotic fibroblast activation (59,60). Acharya et al. (61) showed that CD26/DPP4 was upregulated in proliferating type II alveolar epithelial cells and that CD26 expression in proliferating type II cells was not associated with fibroblast lesions, further supporting the notion that alveolar epithelial injury precedes fibroblast formation. Soare et al. (62) proposed in the literature that DPP4 is characteristic of an activated fibroblast population and regulates TGF-\beta-induced fibroblast activation. DPP4 inhibitors have strong anti-fibrotic effects in well-tolerated doses. DPP4 regulates fibroblast activation and collagen release in vitro and in vivo. In the study by Suzuki et al. (63), the DPP4 inhibitor, vildagliptin, improved PF and LPSinduced lung injury by inhibiting endothelial stromal transformation in a mouse model of PF after systemic endotoxin injury.

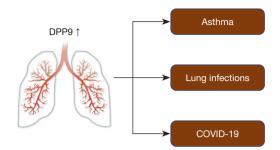
# Association with pulmonary hypertension (PH)

PH, defined as pulmonary artery pressure  $\geq 25 \text{ mmHg}$ , is a chronic cardiopulmonary disease with multiple genetic and pathophysiologic causes, characterized by pulmonary vascular damage and remodeling leading to increased pulmonary vascular resistance and eventual death from right heart failure (64). Vascular inhibition of DPP4 was previously reported to be important for vascular protection (65). In their study, Salheen *et al.* (66) proposed that the DPP4 inhibitor ligliptin significantly reduced vascular superoxide in hyperglycemic conditions and improved endothelium-dependent dilatation. Similarly, chronic hypoxia-induced PH in rats was attenuated. These results suggest that DPP4 inhibition relieves pulmonary arterial remodeling in patients with experimental PH by inhibiting the proliferation and migration of pulmonary smooth muscle cells. DPP4 inhibition as a novel therapeutic approach for pulmonary arterial hypertension led to anti-oxidant, anti-inflammatory, and anti-fibrotic effects, which improved PH (67).

# DPP9 overview

DPP9 (16), an N-terminal dipeptide targeting enzyme with proline, was identified in 2000 and concluded to be located in the cytoplasm due to a lack of transmembrane and secretory signaling. The sequence homology of members of the DPP4 gene family suggests that DPP9 may have DPP4-like activity (68). For DPP9, it has been shown that the longer N-terminal isoform contains nuclear localization signals and preferentially localizes to the nucleus. The similarity between DPP9 and DPP4 in tissue expression patterns and substrates suggests potential roles, such as in T cell activation and immune function (69). DPP9 is ubiquitously expressed at mRNA levels in humans and rodents, including lymphocytes and epithelial cells in many organs, and thus may play a role in the immune system and epithelial cells, as well as in proliferation (70). High expression of DPP9 promotes fibrosis in renal tubular epithelial cells and inhibitors of DPP9 reverse their EMT (71). It has been demonstrated that DPP9 is ratelimiting in the degradation of proline-containing peptides and is involved in antigen delivery (72). Deletion of the DPP9 gene, which substitutes the active site serine for alanine, has been shown to be lethal, resulting in neonatal death within 8-24 hours after birth. Analysis of gene expression patterns in these knockout mice suggests that the proteases involved gene expression differences in cell growth, innate immunity, and metabolic pathways. Although the rate of cleavage was lower than that of DPP4, DPP9 was able to cleave DPP4 substrates in vitro. Given the cytoplasmic location of DPP9, the physiological relevance of the extracellular cleavage of these peptides is unknown. Interestingly, the inhibitory effect of DPP9 on Akt activation is dependent on growth factors, and the effect of DPP9 on Akt does not occur when the activity of the DPP9 kinase is mutated or reduced by inhibition. These results suggest that DPP9 plays an important signaling role in the regulation of survival and proliferation pathways (73). It has been reported that the DPP9 inhibitor 1G244 may be involved in adipogenesis because it impairs adipogenic differentiation. The same inhibitors had anti-inflammatory effects on human and mouse-activated M1 macrophages (74). Other studies have shown that DPP9 is involved in

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**Figure 3** DPP9 mRNA levels are elevated in lung diseases such as asthma, lung infections and COVID-19. DPP, dipeptidyl peptidase; COVID-19, coronavirus disease 2019; mRNA, messenger RNA.

cell migration, apoptosis, and cell adhesion (75). SUMO1 has been identified as an interaction partner of DPP9 and has been shown to act as an allosteric regulator of either SUMO1 or SUMO-mimetic proteins (76). We also found that another partner of DPP9 interaction is the filamin A, which recruits DPP9 to targeted tyrosine kinases (an important component of B cell receptor signaling), which can be cleaved by DPP9 and affecting its stability (77). In recent years, further progress has been made in DPP9 inhibition through activation of apoptosis by the inflammasome sensor protein NLRP1b (78). DPP9 inhibitors were identified to activate all functional NLRP1 alleles in rodents (79) in addition to human NLRP1 and CARD8. Inhibition of DPP9 may trigger the characteristic NLRP1b inflammasome in mouse macrophages.

# Association with pulmonary disease

It has been shown that DPP9 are upregulated enzymatically in experimental asthma in rats. Increased levels of DPP9 mRNA have been reported in inflamed lungs (75) (Figure 3). A significant increase in the expression of DPP9 has been reported in patients with various forms of COVID-19, suggesting that the DPP family, such as DPP9, is a critical immunoregulatory factor. It can be postulated that increased expression of DPP9 in COVID-19 may regulate homeostasis that is detrimental to inflammation (80). Genome-wide association studies identified DPP9 as a susceptibility locus for PF, and in IPF, DPP9 was expressed in fibroblast lesions (81). Tang et al. (82) studied the role of DPP9 inhibition in non-small-cell lung carcinoma and the role of DPP9 in regulating EMT in vitro and in vivo. The results indicate that inhibition of DPP9 expression by small interfering RNA (siRNA) inhibits cell proliferation, migration, and invasion. Upregulation of DPP9 was

significantly associated with advanced TNM staging and had a strong prognostic value for overall survival in patients with non-small cell lung cancer (NSCLC).

#### Conclusions

This review summarizes most of the current evidence that DPP4/9 is associated with lung disease. Within the DPP4 family, the role of DPP4 in particular in respiratory disease is important, however DPP9 has been very popular in recent years, which warrants further exploration of the role of this protease in lung disease and possible new therapies.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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