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# COVID-19 and comorbidities: A role for dipeptidyl peptidase 4 (DPP4) in disease severity?

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## Abstract

The coronavirus disease 2019 (COVID-19) pandemic is caused by a novel betacoronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), similar to SARS-CoV and Middle East respiratory syndrome (MERS-CoV), which cause acute respiratory distress syndrome and case fatalities. COVID-19 disease severity is worse in older obese patients with comorbidities such as diabetes, hypertension, cardiovascular disease, and chronic lung disease. Cell binding and entry of betacoronaviruses is via their surface spike glycoprotein; SARS-CoV binds to the metalloprotease angiotensin-converting enzyme 2 (ACE2), MERS-CoV utilizes dipeptidyl peptidase 4 (DPP4), and recent modeling of the structure of SARS-CoV-2 spike glycoprotein predicts that it can interact with human DPP4 in addition to ACE2. DPP4 is a ubiquitous membrane-bound aminopeptidase that circulates in plasma; it is multifunctional with roles in nutrition, metabolism, and immune and endocrine systems. DPP4 activity differentially regulates glucose homeostasis and inflammation via its enzymatic activity and nonenzymatic immunomodulatory effects. The importance of DPP4 for the medical community has been highlighted by the approval of DPP4 inhibitors, or gliptins, for the treatment of type 2 diabetes mellitus. This review discusses the dysregulation of DPP4 in COVID-19 comorbid conditions; DPP4 activity is higher in older individuals and increased plasma DPP4 is a predictor of the onset of metabolic syndrome. DPP4 upregulation may be a determinant of COVID-19 disease severity, which creates interest regarding the use of gliptins in management of COVID-19. Also, knowledge of the chemistry and biology of DPP4 could be utilized to develop novel therapies to block viral entry of some betacoronaviruses, potentially including SARS-CoV-2.

## KEYWORDS

case fatality, COVID-19, dipeptidyl-peptidase IV inhibitors, metabolic syndrome, SARS-CoV-2

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### Highlights

- Coronavirus disease 2019 (COVID-19) is caused by SARS-CoV-2; recent modeling of the structure of SARS-CoV-2 spike glycoprotein, which mediates viral-host-cell entry, predicts interactions with dipeptidyl peptidase 4 (DPP4) in addition to angiotensin-converting enzyme 2.
- Increased DPP4 expression and activity are associated with diabetes, obesity, and metabolic syndrome, all of which have been reported to influence COVID-19 severity.
- DPP4 inhibitors (gliptins), which vary in their interactions with the active site of the enzyme, may have immunomodulatory and cardioprotective effects that could be beneficial in COVID-19 cases.

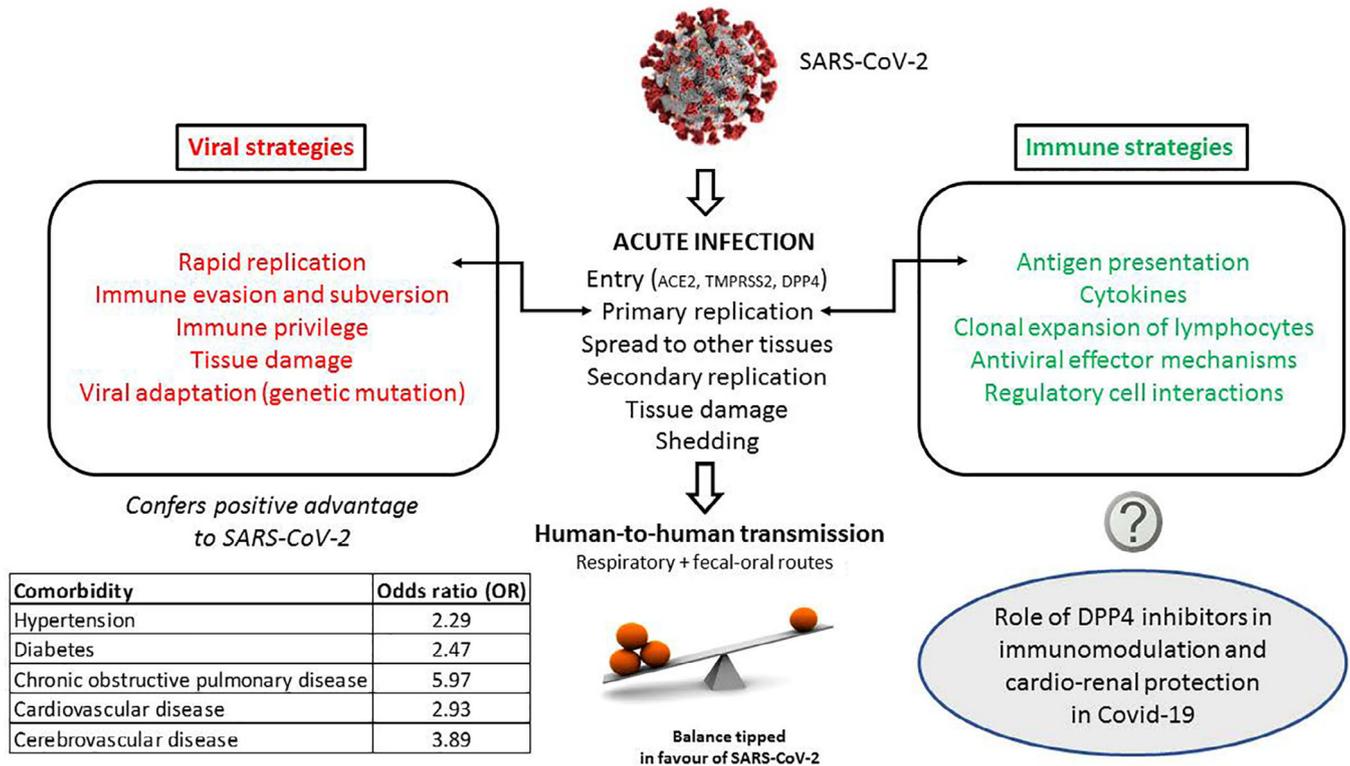
## 1 | INTRODUCTION

The rampant new clinical infectious disease that emerged in late 2019 and rapidly became a world pandemic is caused by a novel betacoronavirus; the disease is now called COVID-19 (Coronavirus Disease 2019). The natural reservoir of these enveloped, single-stranded positive-sense RNA viruses is thought to be bats. The zoonotic potential of betacoronaviruses is well recognized, with species such as pangolins, the most illegally trafficked mammal,<sup>1</sup> civets, and dromedary camels serving as intermediate hosts. The sudden emergence and spread of COVID-19 is similar to severe acute respiratory syndrome (SARS)—a related disease that appeared in 2002 in Asia.<sup>2</sup> Nearly a decade later in 2012 another respiratory syndrome erupted in the Middle East, Middle East respiratory syndrome (MERS), which was also caused by zoonotic transmission of a coronavirus.<sup>3</sup> The coronaviruses that cause these 21st century clinical respiratory syndromes are now classified as SARS coronavirus (SARS-CoV), MERS coronavirus (MERS-CoV), and SARS-CoV-2.

In SARS and MERS cases a number of risk factors were noted to be associated with progression to acute respiratory distress syndrome (ARDS), especially advanced age and male sex. For MERS, additional risk factors included chronic conditions such as diabetes mellitus, hypertension, cardiac diseases, and obesity.<sup>4</sup> A similar picture is emerging with COVID-19. An analysis of 46 248 SARS-CoV-2 infected patients found that the most prevalent comorbidities were hypertension and diabetes, followed by cardiovascular diseases and respiratory system disease. Compared with the nonsevere patient, the pooled odds ratios (OR) of hypertension/diabetes, respiratory system disease and cardiovascular disease in severe patients were OR 2.36, OR 2.46, and OR 3.42 respectively.<sup>5</sup> Another meta-

analysis of six Chinese studies showed the highest odds ratio (5.97) for COVID-19 in patients with preexisting chronic obstructive pulmonary disease (COPD).<sup>6,7</sup> Similarly, a report of 72 314 confirmed and suspected cases of COVID-19 published by the Chinese Centre for Disease Control and Prevention showed increased mortality in people with diabetes (2.3%, overall in 44 672 confirmed cases and 7.3% for patients with diabetes).<sup>8</sup> Italian COVID-19 patients show similar comorbidities; more than two-thirds of the COVID-19 case fatalities had diabetes, cardiovascular diseases, cancer, or were former smokers.<sup>9</sup> Older age and male sex have also been confirmed as important factors in disease severity in a recent meta-analysis.<sup>10</sup> Clinical features of severe COVID-19 include not only acute lung injury but also acute cardiac injury and heart failure, irrespective of whether the patient has a history of hypertension.<sup>11</sup> Acute kidney injury was also associated with mortality in 25% of these 113 deceased COVID-19 patients. The disease can rampage throughout the body, with gastrointestinal symptoms such as diarrhea and seizures in some severe patients.

The course of any acute viral infection is determined by host factors including the immune response and viral strategies to evade that response to establish primary and rapid replication (Figure 1).<sup>12,13</sup> In both SARS and MERS the viral load in those with severe illness was higher than in those with mild disease, and viral shedding in respiratory secretions was more prolonged.<sup>14</sup> This implies that the balance was tipped toward the virus in those with comorbidities. Initial interactions between a virus and host cell are required for productive viral infection and initiation of the viral life cycle. Thus, the host factors required for SARS-CoV-2 - host interactions during attachment, binding, and entry are important not only in vaccine



**FIGURE 1** The course of any acute viral infection is a balance between viral strategies to establish rapid replication and immune strategies to control infection (adapted from<sup>12</sup>). Studies of coronavirus disease 2019 (COVID)-19 cases consistently show that preexisting chronic conditions—hypertension, diabetes, chronic obstructive pulmonary disease, and cardio/cerebrovascular disease—increase the odds of severe disease.<sup>7</sup> Dipeptidyl peptidase 4 (DPP4) dysregulation may be a contributory factor to case fatalities, raising the question of the role of DPP4 inhibitors in COVID-19 management

development but also in disease pathogenesis and treatment.

### 1.1 | Coronavirus (CoV) entry via the spike glycoprotein

Coronavirus entry is via the spike (S) protein, a type I transmembrane glycoprotein, which contains an N-terminal S<sub>1</sub> subunit receptor binding domain (RBD) and a C-terminal S<sub>2</sub> subunit domain that enables membrane fusion. Binding by the S-protein to a receptor causes a conformational change that is necessary for activation by host cell proteases, and both steps are essential for coronavirus infection of a cell.<sup>15</sup>

At the cell surface, a type II transmembrane serine protease, TMPRSS2, activates the SARS coronavirus S protein such that it can then bind to the metalloprotease angiotensin-converting enzyme 2 (ACE2)<sup>16,17</sup>; these proteases are co-expressed by type II pneumocytes. TMPRSS2 dependency occurs in both SARS-CoV and SARS-CoV-2. This is important as TMPRSS2 inhibitors, for example, Camostat, that are already licensed for other indications could be repurposed as antiviral therapy.<sup>17,18</sup> Camostat is being evaluated in Phase I and II clinical

trials (ClinicalTrials.gov Identifier: NCT04321096), with an upper age limit of 110 years to encompass older adults at risk of severe disease. Trials with Nafamostat mesylate (Fusan), licensed in Japan for treatment of acute pancreatitis, are due to start at the University of Tokyo.

MERS-CoV on the other hand utilizes dipeptidyl-peptidase 4 (DPP4), also termed cluster of differentiation 26 (CD26), as its main entry receptor.<sup>19,20</sup> The tetraspanin CD9 facilitates MERS-CoV entry by scaffolding host cell receptors including DPP4.<sup>21</sup> MERS-CoV infection is mediated by the binding of its S1 protein to the β-propeller domain of DPP4; there are 11 critical residues within the β-propeller domain that directly interact with the S1 protein of the virus (reviewed in<sup>22</sup>). Species permissivity to MERS-CoV is governed by both protein sequence and the variable glycosylation of DPP4.<sup>23</sup> Adaptive evolution of the MERS-CoV spike protein has been demonstrated to occur by multiple paths in vitro all of which alter the surface charge of the spike.<sup>24</sup> Human adenosine deaminase (ADA), which binds to extracellular DPP4 of all mammals except rodents,<sup>25,26</sup> has been shown to compete for MERS-CoV binding, acting as a natural antagonist for MERS-CoV infection.<sup>27</sup>

The interaction of MERS-CoV spike protein with DPP4 involves not only the RBD in domain B of the S<sub>1</sub>

subunit but also interactions of domain A with sialylated receptors that facilitate viral entry into airway epithelial cells. It is suggested that this additional attachment factor may also be a determinant of tissue and host tropism.<sup>20</sup> The number of sialylated DPP4 isoforms isolated from human peripheral blood mononuclear cells increases significantly with age greater than 40 years.<sup>28</sup> That study also found that hypersialylation of DPP4 modifies its surface charge, promoting binding of human immunodeficiency virus (HIV) peptides such that certain HIV moieties are likely to engage this phenomenon as an auxiliary adhesion mechanism to fuse with cells.

Recent modeling of the homotrimer structure of SARS-CoV-2 spike protein predicts that the S1 domain binds to human DPP4.<sup>29</sup> The model demonstrated a large binding interface between the SARS-CoV-2 S1 glycoprotein and DPP4 suggesting a tight interaction. It might be that this binding is influenced by the sialylation of DPP4, discussed previously. Other studies have not shown that SARS-CoV-2 binds to DPP4 but have shown that betacoronaviruses are capable of entering human cells through an unknown receptor.<sup>30</sup> There are thus important commonalities between coronaviruses in relation to the first step in the viral life cycle, host cell binding and entry. This review focuses on DPP4 as its expression may be a factor in determining the balance between virus and host in COVID-19 and can potentially be linked to some of the known comorbidities.

## 2 | DIPEPTIDYL-PEPTIDASE 4

The abundant ubiquitous DPP4 protein was first isolated in the 1970s and is now well characterized. It is a 110 kDa glycoprotein, a membrane-bound aminopeptidase that preferentially cleaves peptides containing a proline or alanine residue in the penultimate amino-terminal position. The extracellular domain of homodimeric DPP4 is often cleaved from cell membranes and circulates in plasma, where it remains enzymatically active. DPP4 is multifunctional with roles in nutrition, metabolism, the immune and endocrine systems, bone marrow mobilization, cancer growth, and cell adhesion. The importance of DPP4 for the medical community has been highlighted by the approval of DPP4 inhibitors for the treatment of type 2 diabetes mellitus (T2DM) (reviewed in<sup>31</sup>).

### 2.1 | Tissue distribution of DPP4 and dysregulation in disease(s)

The clinical features of COVID-19 reflect the ability of SARS-Cov-2 to infect different tissues and their

constituent cells, which in turn echoes the expression of viral attachment/binding receptors. Although ACE2 is expressed on pneumocytes and enterocytes of the small intestine,<sup>32</sup> a recent study has shown that the expression on alveolar type 2 cells is rather low compared to other cells expressing ACE2, raising the possibility that SARS-CoV-2 utilizes coreceptors.<sup>33</sup> That study demonstrates ACE2 expression is high in kidney and intestine (esophagus, stomach, ileum, colon, and rectum) and is correlated with expression of other peptidases that are used as entry receptors by coronaviruses. DPP4 was found to be the first gene clustered with ACE2 and, as modeling suggests a tight interaction between SARS-CoV-2 S1 and DPP4,<sup>29</sup> the tissue distribution of DPP4 is relevant.

In the natural reservoir of betacoronaviruses, bats, DPP4 is in epithelial cells of both the respiratory and the intestinal tract of frugivorous bats, similar to humans, but in insectivorous bats it is preferentially expressed in the intestinal tract.<sup>34</sup> This suggests that in some bat species the mode of transmission is via the fecal-oral route. Hence differences in the distribution of DPP4 expression among MERS-CoV susceptible species might influence virus tropism, pathogenesis, and transmission route.

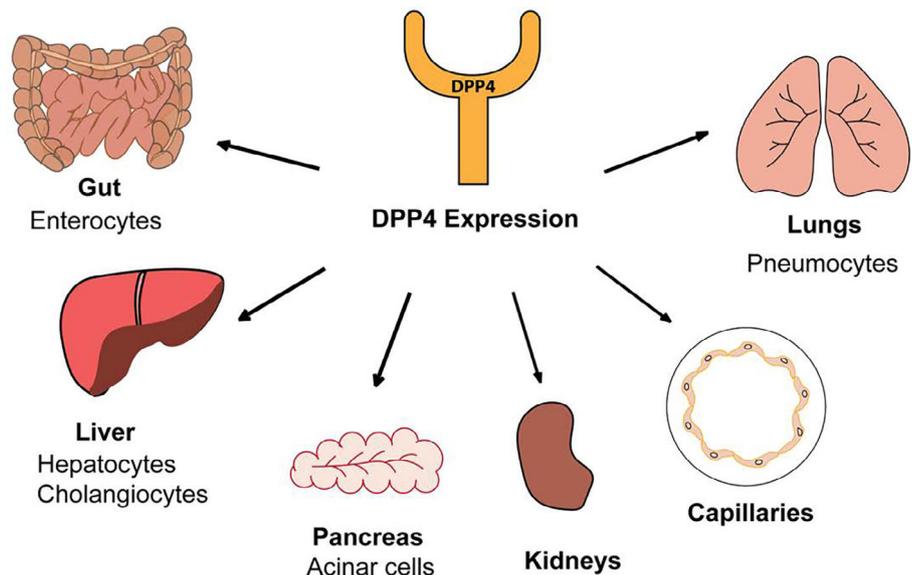
In humans the most intense expression of DPP4 is in salivary gland, kidney, seminal fluid, and liver (Figure 2). DPP4 is also high in enterocytes, particularly colonic enterocytes, as well as blood vessel capillaries, lung epithelium, and immune cells (activated T, B, and natural killer cells and myeloid cells). The level of expression depends on the cell type, differentiation state, and/or the activation state.<sup>35,36</sup> DPP4 activity is in saliva of humans and ferrets<sup>37,38</sup> and mucosal-associated invariant T cells (MAITs) express high levels of CD26/DPP4.<sup>39</sup> SARS-CoV-2 is probably spread by the fecal-oral route in humans and ferrets.<sup>38,40</sup>

DPP4 activity is higher in older individuals compared to younger ones and, *in vitro*, is selectively expressed on the surface of senescent, but not proliferating, human diploid fibroblasts.<sup>41</sup> DPP4 is present in the lower respiratory tract epithelium, mainly on alveolar type 2 cells,<sup>33</sup> but patients with COPD and cystic fibrosis exhibit increased DPP4 not only in these cells but also alveolar macrophages.<sup>42,43</sup> DPP4 upregulation in type I pneumocytes may be a crucial determinant for severe MERS-CoV infection.<sup>22</sup>

The widespread expression of DPP4 on blood capillaries, myocardium, and myeloid cells and the non-enzymatic function of DPP4 as a signaling and binding protein, across a wide range of species, imply a role in angiogenesis, cardiovascular regulation, and inflammation.<sup>44,45</sup> DPP4 inhibition is beneficial in animal models of acute and chronic kidney injury (reviewed in<sup>46</sup>). In patients with different stages of chronic kidney disease



**FIGURE 2** Dipeptidyl peptidase 4 (DPP4) expression on epithelia and endothelium. In humans, DPP4 is strongly expressed on the apical surfaces of polarized epithelium including lung, liver (hepatocytes and cholangiocytes), pancreas (acinar cells), intestine, and kidney tubules. DPP4 is also present on the inner surfaces of capillary endothelial cells. Figure design Michelle Sui Wen Xiang



the activities of both DPP4 and ACE2 correlate with estimated glomerular filtration rates (eGFR).<sup>47</sup> This study of 268 participants found that those with the lowest eGFR exhibited the highest DPP4 and ACE2 activities and that DPP4 also correlated with age.

The liver plays a crucial role by contributing to systemic DPP4 levels. DPP4 is highly expressed in the healthy liver and this expression is increased in liver disease and cirrhosis.<sup>48</sup> Elevated expression of DPP4 in the liver promotes non-alcoholic fatty liver disease (NAFLD) and insulin resistance.<sup>49–51</sup> Glucose-induced expression of DPP4 in the liver is facilitated by demethylation of the DPP4 gene early in life<sup>52</sup> and this epigenetic regulation is responsive to dietary protein restriction.<sup>53</sup> There is important crosstalk between the liver and visceral adipose tissue in obesity-induced metabolic syndrome (MS).<sup>54</sup> In this mouse model obesity stimulates hepatocytes to synthesize and secrete DPP4, which acts with plasma factor Xa to increase inflammation in adipose tissue. Adipose tissue is also a relevant source of DPP4 in diet-induced obesity<sup>55</sup> and is involved in linking obesity to MS.<sup>56,57</sup> Obese individuals have higher circulating levels of DPP4<sup>57</sup> and the level is correlated with body mass index (BMI) in young healthy people.<sup>58</sup>

## 2.2 | DPP4, immunomodulation, and infection

DPP4 also possesses noncatalytic functions through its interaction with ligands, primarily ADA.<sup>25</sup> DPP4 is a co-stimulator for T cell activation by binding to ADA and additionally enhances lymphocyte proliferation

independent of ADA binding.<sup>59</sup> As adenosine is a potent suppressor of T cell proliferation, inducing its degradation through increased DPP4 activity can increase T cell proliferation. Obese humans demonstrate increased levels of DPP4 expression in dendritic cell/macrophage cell populations from visceral adipose tissue, potentiating inflammation in obesity by interacting with ADA.<sup>60</sup> Hence increased DPP4 in conditions such as obesity-induced MS results in failure to resolve inflammation and chronic subclinical activation of the immune system. This metabolic/immune dysregulation may provide the “ideal home” for some coronavirus infections.

The adenosine nucleoside analogue, galidesivir (BCX4430), which has broad-spectrum activity against a wide range of RNA viruses, including flaviviruses such as Zika,<sup>61</sup> is now being evaluated in COVID-19 (ClinicalTrials.gov Identifier: NCT03891420). The rationale is that it acts to block viral RNA-dependent RNA polymerase, which plays a crucial role in the viral replication process. It is unknown how such a therapy could interact with the immunoregulatory, mostly anti-inflammatory, effects of adenosine in different immune cell types<sup>62</sup> and how increased DPP4 expression and chronic subclinical inflammation in obesity-induced MS will affect the clinical response.

DPP4 has identified roles in other infections. In chronic hepatitis C virus (HCV), DPP4 generates an antagonist form of the chemokine CXCL10 (also known as IP-10) by amino-terminal truncation of the protein,<sup>63</sup> such that the elevated plasma CXCL10 found in patients with chronic HCV can modulate immune responses by chemokine receptor antagonism.<sup>64</sup> CXCR3 antagonism via truncated CXCL10 may also be an important

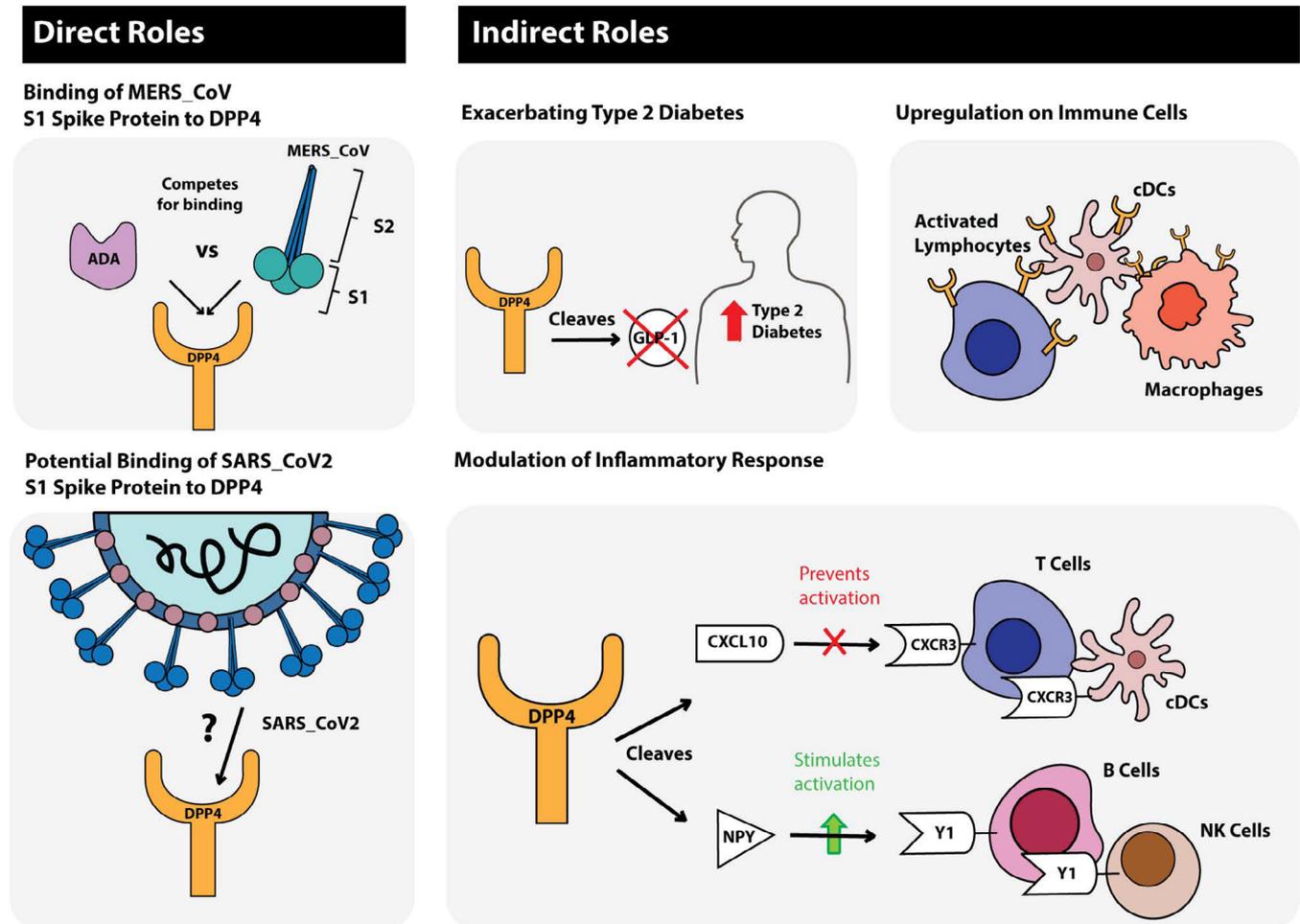
regulatory mechanism occurring in tumours<sup>65</sup> and in sites of tuberculosis pathology.<sup>64</sup>

### 3 | COVID-19 COMORBIDITIES, DISEASE MANIFESTATIONS, AND SEVERITY

Older age and comorbidities play important roles in influencing the severity of COVID-19. In one study the incidences of hypertension, cardio-cerebrovascular diseases, and diabetes mellitus (DM) were 2-3-fold higher in intensive care unit (ICU)/severe cases than in their non-ICU/severe counterparts.<sup>66</sup> In individuals with DM but without other comorbidities, serum levels of inflammation-related biomarkers such as interleukin (IL)-6, C-reactive protein, serum ferritin and coagulation

index, and D-dimer, were significantly higher ( $P < .01$ ) compared with those without DM, suggesting that patients with diabetes are more susceptible to an inflammatory storm eventually leading to rapid deterioration and increased mortality.<sup>8,67</sup> As approximately 425 million adults (1 in 11) are living with diabetes, therapeutic options in diabetes become important.

In a French study of 124 consecutive hospitalized COVID-19 patients, obesity (BMI  $>30$  kg/m<sup>2</sup>) and severe obesity (BMI  $>35$  kg/m<sup>2</sup>) were present in 47.6% and 28.2% of cases, respectively.<sup>68</sup> The need for invasive mechanical ventilation was significantly associated with male sex ( $P < .05$ ) and BMI ( $P < .05$ ), independent of age, diabetes, and hypertension. As noted previously, increased DPP4 expression and activity are associated with obesity and MS.<sup>54,57,58,69</sup> Hence extensive emerging data is pointing to an important direct metabolic and



**FIGURE 3** Potential roles of dipeptidyl peptidase 4 (DPP4) in COVID-19. DPP4 contributes to pathogenesis in type 2 diabetes mellitus via cleavage of GLP-1. DPP4 has roles in inflammation and immunity. Adenosine deaminase (ADA) binds to DPP4 on the same site that the Middle East respiratory syndrome (MERS-CoV) S1 protein binds to DPP4. DPP4 is on macrophages and classical dendritic cells (cDC) and is upregulated on activated lymphocytes. DPP4 cleaves CXCL10, which prevents its binding to CXCR3 on T cells and cDC. DPP4 cleaves NPY, which is able to stimulate NK and B cells. The S1 Spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is predicted to bind to DPP4, which may facilitate infection of epithelia. Figure design Michelle Sui Wen Xiang



endocrine mechanistic link to the viral disease process (Figure 3) leading to the suggestion that more attention should be paid to the treatment of comorbidities in COVID-19 as these patients often die.<sup>6</sup>

#### 4 | DPP4 INHIBITION

DPP4 inhibitors, also known as gliptins, are now a firmly established class of oral antidiabetic agents for the treatment of T2DM (reviewed in<sup>70</sup>). The gliptins are not a homogenous class of compounds but show different interactions with the active site of the enzyme molecule.<sup>31,70</sup> The gliptins are classified into three classes depending on their mode of binding.<sup>71</sup> Eight DPP4 inhibitors are currently approved for T2DM, some only in Japan and Korea. For example teneligliptin, which was developed in Japan, has a unique structure characterized by a J-shape and an anchor-lock domain and not only has strong DPP4 inhibitory function but also is safe for patients with end-stage renal disease.<sup>72</sup>

As modeling suggests that DPP4 is a co-receptor for SARS-CoV-2 viral entry<sup>29</sup> and disease severity in COVID-19 is associated with conditions in which there is dysregulation of DPP4, the role of DPP4 inhibition in the COVID-19 disease process needs to be explored.

Although the gliptins do not bind to the putative receptor binding site of SARS-CoV-2, research over the past two decades toward drug discovery of the gliptins has yielded vast knowledge of the chemistry and biology of DPP4 and its binding interactions<sup>26,31,71</sup>; this could be utilized in developing new anticoronavirus drugs. It is feasible that a therapy could be designed to shield the human viral entry protein(s) from the virus, using an antibody or peptide that binds to the human protein. A therapeutic vaccine to human DPP4 has already been developed as a novel potential therapy for T2DM.<sup>73</sup> Pang et al selected three suitable regions in DPP4 as candidate targets for a vaccine and conjugated these peptides to the adjuvant, keyhole limpet hemocyanin, which presents a variety of T cell epitopes to induce helper T cell responses and demonstrated its efficacy in improving the diabetic phenotype in animal models.

Altered DPP4 expression in comorbid conditions of COVID-19 may favor the virus in ways that are not currently understood. There is a possibility not only that gliptins may modulate the severity of COVID-19 but also each DPP4 inhibitor/class may have differential effect(s). It would be of interest to compare the diabetic (and other) therapy in those with severe vs nonsevere disease.<sup>8</sup> For example, in Japan a DPP4 inhibitor was chosen as initial monotherapy in the majority of T2DM patients (1410/2666 patients), a decision influenced by older

age.<sup>74</sup> Does such therapy influence severity of COVID-19 compared to treatment with a sulfonylurea or a biguanide? Would the addition of a DPP4 inhibitor improve the hyperglycemia and inflammatory activation in older patients with COVID-19? Are any potential beneficial effects of gliptins outweighed by treatment with ACE inhibitors, which increase ACE2 expression in diabetics?<sup>75</sup> It is unclear whether the use of renin-angiotensin-aldosterone system inhibitors alone have potential for more benefit than harm in patients with COVID-19.<sup>76</sup> Data collected during this pandemic need to be interrogated for medicinal drug usage and interactions in all groups with comorbidities.

In rodent models, different gliptins have been shown to have a variety of effects that could be beneficial in COVID-19 pathology. Thus, vildagliptin and saxagliptin have significant anti-inflammatory activity comparable to that of aspirin in an acute model of inflammation.<sup>77</sup> Saxagliptin-mediated DPP4 inhibition can attenuate DM-induced activation of the NLRP3 inflammasome and reduce the serum levels of CRP, tumor necrosis factor  $\alpha$ , IL-1 $\beta$ , IL-18, and IL-6.<sup>78</sup> There is also evidence of crosstalk between DPP4 and the renin-angiotensin system in the pathophysiology of cardiorenal syndromes and that gliptins are cardioprotective and may delay the onset of cardiovascular impairment in chronic kidney disease.<sup>46,79</sup> Likewise, gliptins may have a role in treatment of the hepatic manifestation of obesity-induced metabolic syndrome, NAFLD.<sup>80,81</sup>

In patients, gliptins exert a comprehensive and potent anti-inflammatory effect; it has been shown for example that sitagliptin treatment not only causes a significant fall of plasma concentrations of C-reactive protein (CRP) and IL-6 but also suppressed the mRNA expression of CD26/DPP4 in mononuclear cells by  $16 \pm 6\%$  within 2 hours after a single dose.<sup>82</sup> Mathematical modeling indicates that the spread of MERS-CoV infection could be controlled by decreasing the expression of DPP4.<sup>83</sup> Hence, if DPP4 expression facilitates infection by SARS-CoV-2, perhaps the anti-inflammatory activity of clinically used DPP4 inhibitors<sup>84</sup> could be repurposed to treat COVID-19 patients, especially those with elevated blood glucose, markers of virally driven hyperinflammation<sup>85,86</sup> or cardiorenal problems.<sup>46</sup>

Another question to ask is whether known genetic variation(s) in *DPP4*<sup>87</sup> affect viral entry and attenuate viral replication, as has been noted for MERS.<sup>88</sup>

#### 5 | CONCLUSIONS

At the time of writing SARS-CoV-2 has infected >3.75 million people in 187 countries, leading to at least 265 000 deaths and the numbers of COVID-19 cases

continue to rise exponentially worldwide. Comorbid conditions that include obesity-induced metabolic syndrome and associated T2DM influence disease severity. T2DM has itself been called a pandemic with around 415 million adults living with the disease. As a higher proportion of these individuals can expect to become critically ill when infected with SARS-CoV-2 it is important not only to ask why but also to optimize treatment regimens.

In this review we focus on DPP4 as recent modeling of the structure of SARS-CoV-2 spike glycoprotein, which mediates viral-host-cell binding and entry, predicts that it interacts with human DPP4 in addition to ACE2. Furthermore, increased DPP4 expression and activity have been consistently associated with obesity, T2DM, and diabetes complications. DPP4 inhibitors, also known as gliptins, are now a firmly established class of oral antidiabetic agents for the treatment of T2DM. It is important to understand whether some or all gliptins modulate COVID-19 disease severity, possibly via their immunomodulatory and cardioprotective effects. Finally, although gliptins do not bind to the putative binding site of SARS-CoV-2, it may be that the vast knowledge of the biology and biochemistry of DPP4 and other proteases that has accumulated over past decades could be utilized in the development of novel therapies to block viral entry and in vaccine design.

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## DISCLOSURES

None declared.

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## REFERENCES

- Lam TT, Shum MH, Zhu HC, et al. Identifying SARS-CoV-2 related coronaviruses in Malayan pangolins. *Nature*. 2020. [Epub ahead of print].
- Zhong NS, Zheng BJ, Li YM, et al. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. *Lancet*. 2003;362(9393):1353-1358.
- de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol*. 2016;14(8):523-534.
- Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. *Int J Infect Dis*. 2016;49:129-133.
- Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *Int J Infect Dis*. 2020;94:91-95.
- Wang T, Du Z, Zhu F, et al. Comorbidities and multi-organ injuries in the treatment of COVID-19. *Lancet*. 2020;395(10228):e52.
- Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging*. 2020;12(7):6049-6057.
- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239.
- Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet*. 2020;395(10231):1225-1228.
- Rodriguez-Morales AJ, Cardona-Ospina JA, Gutierrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: a systematic review and meta-analysis. *Travel Med Infect Dis*. 2020;34:101623.
- Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091.
- Virgin HW, Wherry EJ, Ahmed R. Redefining chronic viral infection. *Cell*. 2009;138(1):30-50.
- Mandl JN, Ahmed R, Barreiro LB, et al. Reservoir host immune responses to emerging zoonotic viruses. *Cell*. 2015;160(1-2):20-35.
- Oh MD, Park WB, Choe PG, et al. Viral load kinetics of MERS coronavirus infection. *N Engl J Med*. 2016;375(13):1303-1305.
- Simmons G, Zmora P, Gierer S, Heurich A, Pohlmann S. Proteolytic activation of the SARS-coronavirus spike protein: cutting enzymes at the cutting edge of antiviral research. *Antiviral Res*. 2013;100(3):605-614.
- Glowacka I, Bertram S, Muller MA, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. *J Virol*. 2011;85(9):4122-4134.
- Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181:271-280.e8.
- Zhou Y, Vedantham P, Lu K, et al. Protease inhibitors targeting coronavirus and filovirus entry. *Antiviral Res*. 2015;116:76-84.
- Raj VS, Mou H, Smits SL, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. *Nature*. 2013;495(7440):251-254.
- Park YJ, Walls AC, Wang Z, et al. Structures of MERS-CoV spike glycoprotein in complex with sialoside attachment receptors. *Nat Struct Mol Biol*. 2019;26(12):1151-1157.
- Earnest JT, Hantak MP, Li K, McCray PB Jr, Perlman S, Gallagher T. The tetraspanin CD9 facilitates MERS-coronavirus entry by scaffolding host cell receptors and proteases. *PLoS Pathog*. 2017;13(7):e1006546.

22. Widagdo W, Sooksawasdi N, Ayudhya S, Hundie GB, Haagmans BL. Host determinants of MERS-CoV transmission and pathogenesis. *Viruses*. 2019;11(3):280.
23. Peck KM, Scobey T, Swanstrom J, et al. Permissivity of dipeptidyl peptidase 4 Orthologs to Middle East respiratory syndrome coronavirus is governed by glycosylation and other complex determinants. *J Virol*. 2017;91(19):e00534–17.
24. Letko M, Miazgowicz K, McMinn R, et al. Adaptive evolution of MERS-CoV to species variation in DPP4. *Cell Rep*. 2018;24(7):1730–1737.
25. Abbott CA, McCaughan GW, Levy MT, Church WB, Gorrell MD. Binding to human dipeptidyl peptidase IV by adenosine deaminase and antibodies that inhibit ligand binding involves overlapping, discontinuous sites on a predicted beta propeller domain. *Eur J Biochem*. 1999;266(3):798–810.
26. Gorrell MD. Dipeptidyl peptidase IV and related enzymes in cell biology and liver disorders. *Clin Sci (Lond)*. 2005;108(4):277–292.
27. Raj VS, Smits SL, Provacia LB, et al. Adenosine deaminase acts as a natural antagonist for dipeptidyl peptidase 4-mediated entry of the Middle East respiratory syndrome coronavirus. *J Virol*. 2014;88(3):1834–1838.
28. Smith RE, Talhouk JW, Brown EE, Edgar SE. The significance of hypersialylation of dipeptidyl peptidase IV (CD26) in the inhibition of its activity by tat and other cationic peptides. CD26: a subverted adhesion molecule for HIV peptide binding. *AIDS Res Hum Retroviruses*. 1998;14(10):851–868.
29. Vankadari N, Wilce JA. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. *Emerg Microbes Infect*. 2020;9(1):601–604.
30. Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol*. 2020;5(4):562–569.
31. Kirby M, Yu DM, O'Connor S, Gorrell MD. Inhibitor selectivity in the clinical application of dipeptidyl peptidase-4 inhibition. *Clin Sci (Lond)*. 2009;118(1):31–41.
32. To KF, Lo AW. Exploring the pathogenesis of severe acute respiratory syndrome (SARS): the tissue distribution of the coronavirus (SARS-CoV) and its putative receptor, angiotensin-converting enzyme 2 (ACE2). *J Pathol*. 2004;203(3):740–743.
33. Qi F, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem Biophys Res Commun*. 2020;526:135–140.
34. Widagdo W, Begeman L, Schipper D, et al. Tissue distribution of the MERS-coronavirus receptor in bats. *Sci Rep*. 2017;7(1):1193.
35. Cook SJ, Lee Q, Wong AC, et al. Differential chemokine receptor expression and usage by pre-cDC1 and pre-cDC2. *Immunol Cell Biol*. 2018;96(10):1131–1139.
36. Gorrell MD, Gysbers V, McCaughan GW. CD26: a multifunctional integral membrane and secreted protein of activated lymphocytes. *Scand J Immunol*. 2001;54(3):249–264.
37. Aemaimanan P, Sattayasai N, Wara-aswapati N, et al. Alanine aminopeptidase and dipeptidyl peptidase IV in saliva of chronic periodontitis patients. *J Periodontol*. 2009;80(11):1809–1814.
38. Kim YI, Kim SG, Kim SM, et al. Infection and rapid transmission of SARS-CoV-2 in ferrets. *Cell Host Microbe*. 2020:704–709.
39. Sharma PK, Wong EB, Napier RJ, et al. High expression of CD26 accurately identifies human bacteria-reactive MR1-restricted MAIT cells. *Immunology*. 2015;145(3):443–453.
40. Zhang W, Du RH, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. *Emerg Microbes Infect*. 2020;9(1):386–389.
41. Kim KM, Noh JH, Bodogai M, et al. Identification of senescent cell surface targetable protein DPP4. *Genes Dev*. 2017;31(15):1529–1534.
42. Meyerholz DK, Lambertz AM, McCray PB Jr. Dipeptidyl peptidase 4 distribution in the human respiratory tract: implications for the Middle East respiratory syndrome. *Am J Pathol*. 2016;186(1):78–86.
43. Seys LJM, Widagdo W, Verhamme FM, et al. DPP4, the Middle East respiratory syndrome coronavirus receptor, is upregulated in lungs of smokers and chronic obstructive pulmonary disease patients. *Clin Infect Dis*. 2018;66(1):45–53.
44. Zhong J, Maiseyeu A, Davis SN, Rajagopalan S. DPP4 in cardiometabolic disease: recent insights from the laboratory and clinical trials of DPP4 inhibition. *Circ Res*. 2015;116(8):1491–1504.
45. Noels H, Bernhagen J. Editorial: the CXCR4 ligand/receptor family and the DPP4 protease in high-risk cardiovascular patients. *Front Immunol*. 2016;7:58.
46. Nistala R, Savin V. Diabetes, hypertension, and chronic kidney disease progression: role of DPP4. *Am J Physiol Renal Physiol*. 2017;312(4):F661–F670.
47. Wolke C, Teumer A, Endlich K, et al. Serum protease activity in chronic kidney disease patients: the GANI\_MED renal cohort. *Exp Biol Med (Maywood)*. 2017;242(5):554–563.
48. Itou M, Kawaguchi T, Taniguchi E, Sata M. Dipeptidyl peptidase-4: a key player in chronic liver disease. *World J Gastroenterol*. 2013;19(15):2298–2306.
49. Baumeier C, Schluter L, Saussenthaler S, et al. Elevated hepatic DPP4 activity promotes insulin resistance and non-alcoholic fatty liver disease. *Mol Metab*. 2017;6(10):1254–1263.
50. Williams KH, Vieira De Ribeiro AJ, Prakoso E, et al. Circulating dipeptidyl peptidase-4 activity correlates with measures of hepatocyte apoptosis and fibrosis in non-alcoholic fatty liver disease in type 2 diabetes mellitus and obesity: a dual cohort cross-sectional study. *J Diabetes*. 2015;7(6):809–819.
51. Zheng T, Chen B, Yang L, et al. Association of plasma dipeptidyl peptidase-4 activity with non-alcoholic fatty liver disease in nondiabetic Chinese population. *Metabolism*. 2017;73:125–134.
52. Baumeier C, Saussenthaler S, Kammel A, et al. Hepatic DPP4 DNA methylation associates with fatty liver. *Diabetes*. 2017;66(1):25–35.
53. Saussenthaler S, Ouni M, Baumeier C, et al. Epigenetic regulation of hepatic Dpp4 expression in response to dietary protein. *J Nutr Biochem*. 2019;63:109–116.
54. Ghorpade DS, Ozcan L, Zheng Z, et al. Hepatocyte-secreted DPP4 in obesity promotes adipose inflammation and insulin resistance. *Nature*. 2018;555(7698):673–677.
55. Romacho T, Sell H, Indrakusuma I, et al. DPP4 deletion in adipose tissue improves hepatic insulin sensitivity in diet-induced obesity. *Am J Physiol Endocrinol Metab*. 2020;318(5):E590–E599.
56. Lamers D, Famulla S, Wronkowitz N, et al. Dipeptidyl peptidase 4 is a novel adipokine potentially linking obesity to the metabolic syndrome. *Diabetes*. 2011;60(7):1917–1925.
57. Stengel A, Goebel-Stengel M, Teuffel P, et al. Obese patients have higher circulating protein levels of dipeptidyl peptidase IV. *Peptides*. 2014;61:75–82.



58. Kirino Y, Sei M, Kawazoe K, Minakuchi K, Sato Y. Plasma dipeptidyl peptidase 4 activity correlates with body mass index and the plasma adiponectin concentration in healthy young people. *Endocr J*. 2012;59(10):949-953.
59. Yu DM, Slaitini L, Gysbers V, et al. Soluble CD26 / dipeptidyl peptidase IV enhances human lymphocyte proliferation in vitro independent of dipeptidyl peptidase enzyme activity and adenosine deaminase binding. *Scand J Immunol*. 2011;73(2):102-111.
60. Zhong J, Rao X, Deiuiliis J, et al. A potential role for dendritic cell/macrophage-expressing DPP4 in obesity-induced visceral inflammation. *Diabetes*. 2013;62(1):149-157.
61. Julander JG, Siddharthan V, Evans J, et al. Efficacy of the broad-spectrum antiviral compound BCX4430 against Zika virus in cell culture and in a mouse model. *Antiviral Res*. 2017;137:14-22.
62. Antonioli L, Fornai M, Blandizzi C, Pacher P, Hasko G. Adenosine signaling and the immune system: when a lot could be too much. *Immunol Lett*. 2019;205:9-15.
63. Casrouge A, Decalf J, Ahloulay M, et al. Evidence for an antagonist form of the chemokine CXCL10 in patients chronically infected with HCV. *J Clin Invest*. 2011;121(1):308-317.
64. Ragab D, Laird M, Duffy D, et al. CXCL10 antagonism and plasma sDPP4V correlate with increasing liver disease in chronic HCV genotype 4 infected patients. *Cytokine*. 2013;63(2):105-112.
65. Rainczuk A, Rao JR, Gathercole JL, et al. Evidence for the antagonistic form of CXC-motif chemokine CXCL10 in serous epithelial ovarian tumours. *Int J Cancer*. 2014;134(3):530-541.
66. Li B, Yang J, Zhao F, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020;109:531-538.
67. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*. 2020;e3319. [Epub ahead of print].
68. Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity*. 2020. [Epub ahead of print]
69. Yang F, Zheng T, Gao Y, et al. Increased plasma DPP4 activity is an independent predictor of the onset of metabolic syndrome in Chinese over 4 years: result from the China National Diabetes and metabolic disorders study. *PLoS One*. 2014;9(3):e92222.
70. Gallwitz B. Clinical use of DPP-4 inhibitors. *Front Endocrinol*. 2019;10:389.
71. Kushwaha RN, Haq W, Katti SB. Sixteen-years of clinically relevant dipeptidyl peptidase-IV (DPP-IV) inhibitors for treatment of type-2 diabetes: a perspective. *Curr Med Chem*. 2014;21(35):4013-4045.
72. Li X, Huang X, Bai C, et al. Efficacy and safety of tenepligiptin in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol*. 2018;9:449.
73. Pang Z, Nakagami H, Osako MK, et al. Therapeutic vaccine against DPP4 improves glucose metabolism in mice. *Proc Natl Acad Sci U S A*. 2014;111(13):E1256-E1263.
74. Fujihara K, Igarashi R, Matsunaga S, et al. Comparison of baseline characteristics and clinical course in Japanese patients with type 2 diabetes among whom different types of oral hypoglycemic agents were chosen by diabetes specialists as initial monotherapy (JDDM 42). *Medicine*. 2017;96(7):e6122.
75. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8(4):e21.
76. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-angiotensin-aldosterone system inhibitors in patients with COVID-19. *N Engl J Med*. 2020;382:1653-1659.
77. Kagal UA, Angadi NB, Matule SM. Effect of dipeptidyl peptidase 4 inhibitors on acute and subacute models of inflammation in male Wistar rats: an experimental study. *Int J Appl Basic Med Res*. 2017;7(1):26-31.
78. Birnbaum Y, Bajaj M, Qian J, Ye Y. Dipeptidyl peptidase-4 inhibition by Saxagliptin prevents inflammation and renal injury by targeting the Nlrp3/ASC inflammasome. *BMJ Open Diabetes Res Care*. 2016;4(1):e000227.
79. Beraldo JI, Benetti A, Borges-Junior FA, et al. Cardioprotection conferred by Sitagliptin is associated with reduced cardiac angiotensin II/angiotensin-(1-7) balance in experimental chronic kidney disease. *Int J Mol Sci*. 2019;20(8):1940.
80. Schuppan D, Gorrell MD, Klein T, Mark M, Afdhal NH. The challenge of developing novel pharmacological therapies for non-alcoholic steatohepatitis. *Liver Int*. 2010;30(6):795-808.
81. Tacelli M, Celsa C, Magro B, et al. Antidiabetic drugs in NAFLD: the accomplishment of two goals at once? *Pharmaceuticals (Basel)*. 2018;11(4):121.
82. Makdissi A, Ghanim H, Vora M, et al. Sitagliptin exerts an antiinflammatory action. *J Clin Endocrinol Metab*. 2012;97(9):3333-3341.
83. Tang S, Ma W, Bai P. A novel dynamic model describing the spread of the MERS-CoV and the expression of dipeptidyl peptidase 4. *Comput Math Methods Med*. 2017;2017:5285810.
84. Tomovic K, Lazarevic J, Kocic G, Deljanin-Ilic M, Anderluh M, Smelcerovic A. Mechanisms and pathways of anti-inflammatory activity of DPP-4 inhibitors in cardiovascular and renal protection. *Med Res Rev*. 2019;39(1):404-422.
85. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034.
86. Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. *J Med Virol*. 2020. [Epub ahead of print].
87. Jiang L, Yin J, Ye L, et al. Novel risk loci for rheumatoid arthritis in Han Chinese and congruence with risk variants in Europeans. *Arthritis Rheumatol*. 2014;66(5):1121-1132.
88. Kleine-Weber H, Schroeder S, Kruger N, et al. Polymorphisms in dipeptidyl peptidase 4 reduce host cell entry of Middle East respiratory syndrome coronavirus. *Emerg Microbes Infect*. 2020;9(1):155-168.

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