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PERSPECTIVES

Dipeptidyl peptidase-4 (DPP4) inhibition in COVID-19

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Abstract

Aims SARS–CoV-2 causes severe respiratory syndrome (COVID-19) with high mortality due to a direct cytotoxic viral effect and a severe systemic inflammation. We are herein discussing a possible novel therapeutic tool for COVID-19.

Methods Virus binds to the cell surface receptor ACE2; indeed, recent evidences suggested that SARS–CoV-2 may be using as co-receptor, when entering the cells, the same one used by MERS–Co-V, namely the DPP4/CD26 receptor. The aforementioned observation underlined that mechanism of cell entry is supposedly similar among different coronavirus, that the co-expression of ACE2 and DPP4/CD26 could identify those cells targeted by different human coronaviruses and that clinical complications may be similar.

Results The DPP4 family/system was implicated in various physiological processes and diseases of the immune system, and DPP4/CD26 is variously expressed on epithelia and endothelia of the systemic vasculature, lung, kidney, small intestine and heart. In particular, DPP4 distribution in the human respiratory tract may facilitate the entrance of the virus into the airway tract itself and could contribute to the development of cytokine storm and immunopathology in causing fatal COVID-19 pneumonia.

Conclusions The use of DPP4 inhibitors, such as gliptins, in patients with COVID-19 with, or even without, type 2 diabetes, may offer a simple way to reduce the virus entry and replication into the airways and to hamper the sustained cytokine storm and inflammation within the lung in patients diagnosed with COVID-19 infection.

Keywords DPP4 inhibitors · Pneumonia · Diabetes · SARS–CoV-2 · Cytokine storm

Introduction

The novel beta-coronavirus 2019 (SARS–CoV-2) has recently emerged as a threat for human kind, causing severe respiratory syndrome (COVID-19), associated with other systemic complications (i.e., intestinal infections, renal and heart failure) and with a relative high mortality [1]. This pathology has emerged from Wuhan City, in the China region of Hubei, and then spreading in Europe, Asia and USA [1]. This new pandemia follows the severe acute coronavirus respiratory syndrome of 2002–2003 (SARS–CoV), observed in the Guangdong Province of China and the Middle East respiratory syndrome coronavirus of 2012 (MERS–Co-V), mainly affecting the Arabian peninsula [1].

Coronaviruses tropism is primarily determined by the ability of the spike (S) entry glycoprotein to bind to a cell surface receptor. It is well reported now that SARS–CoV-2 may use angiotensin-converting enzyme 2 (ACE2), the same receptor of SARS–CoV, to infect humans [2]. However, recent evidences demonstrated that SARS–CoV-2 binds to

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DPP4/CD26 when entering into cells of the respiratory tract [3]. It appears that the interaction between SARS–CoV-2 spike glycoprotein and the human DPP4/CD26, also known as dipeptidyl peptidase-4 (DPP4), is a key factor for the hijacking and virulence [3]. Interestingly, another recent study clearly reported a correlation between DPP4 and ACE2, suggesting that both membrane proteins are relevant in the pathogenesis of virus entry [4]. The co-expression of ACE2 and DPP4/CD26 as receptors of spike glycoproteins could hypothesize that different human coronaviruses (CoVs) target similar cell types across different human tissues and explain the presence of similar clinical features in patients infected with different CoVs. In another case, it was shown that DPP4 acted for CoV co-receptor, thus suggesting a potential similar mechanism of entry for SARS–CoV-2 [5].

Dipeptidyl peptidase-4 (DPP4), also known as CD26, is a widely expressed serine membrane-anchored ectopeptidase that exists on the surface of different cell types and cleaves dipeptides from the N-terminus, where a proline residue is in a penultimate position [6]. Besides its catalytic activity, DPP4 also acts as a binding protein and a ligand of extracellular factors and a large number of molecules can be cleaved by DPP4. This peptidase transmits intracellular signals through a small intracellular tail that cleave proline and more rapidly alanine and glycine [7, 8]. In particular, post-translational N-terminal hypersialylation may be implicated in DPP4 trafficking and virus aggressivity [9, 10] and, as already demonstrated in MERS–Co-V and porcine respiratory coronavirus, could involve the *N*-glycan binding interfaces of DPP4 [11].

Clinical and experimental research over the past 30 years has clearly suggested that the DPP4/CD26 pathway is involved in various physiological processes and diseases of the immune system [12]; not surprising for a molecule as CD26 that was originally described as a surface marker of T lymphocytes [13]. DPP4/CD26 transmembrane glycoprotein is not only expressed by various cells of the immune system, but also by epithelial and endothelial cells of systemic vasculature, by the endothelial cells of venules and capillaries, by the kidney, small intestine, lung, pancreas, spleen and heart, by the vascular smooth muscle cells, and by monocytes and hepatocytes and is soluble in the plasma [6, 7, 14]. In rats, lung appeared to be organ with the second highest expression of DDP4/CD26 [15]; in particular, lung parenchyma, interstitium and pleural mesothelia were shown to be relative rich in DPP4 protein and are the lung area most affected by the CoVs-related injuries [16, 17]. The relation between DPP4/CD26 expression and site of CoVs-related injuries is overall well demonstrated in MERS–Co-V infection, where DPP4 could directly influence the kinetic of lung inflammation and may act itself as a proinflammatory signaling molecule [16, 18]. In COVID-19, although lacking of extensive pathological data, it appeared to be confirmed the aforementioned dynamic of correlation between DPP4/CD26 localization and site of lung inflammation [3]. Interestingly, both MERS–Co-V and SARS–CoV-2 predominantly infect lower airways and may cause acute respiratory distress syndrome (ARDS) and irreversible fatal pneumonia [17, 19, 20]. Furthermore, both SARS–CoV and MERS–Co-V are characterized by an important cytokine storm, with a similar immunopathology [21]. Virus infection and replication cause delayed interferon response, severe inflammatory monocyte macrophage and neutrophil infiltration and uncontrolled flood of proinflammatory cytokines and chemokines [22]. Moreover, there are evidences of diffuse vascular leakage, endothelial and epithelial apoptosis and of a diffuse microangiopathy with ischemic and thrombotic lesions that induce alveolar edema and collapse [22]. This may be a dramatic link between COVID-19 and diabetes, because the latter are more susceptible to abnormal coagulation and fibrinolysis, to impaired tissue remodeling and to multiorgan fibrosis and failure [23–27]. Taken together, all these findings clearly indicated that the aggressive impact of CoVs (SARS–CoV, MERS–Co-V and COVID-19) on tissues and organs is preferentially modulated, or least co-modulated, by DPP4/CD26 [28] and that DPP4/CD26 inhibition could antagonize this mechanism. DPP4/CD26 system modulation may be one of the new approaches to be employed for the pharmacologic treatment of COVID-19. The large amount of data available on the use of DPP4 inhibitors could support us to give a new strategic direction in COVID-19 treatment [6, 12, 29–33]. The pharmacological possibility to inhibit DPP4/CD26 activity by using commercial DPP4 inhibitors or gliptins (e.g., sitagliptin, linagliptin, vildagliptin and others) may represent a valid weapon to block the host CD26 receptor, thus disabling SARS–CoV-2 way to enter T cells [3, 34]. Along this line of investigation, we recently started at Sacco Hospital in Milan and at San Matteo Hospital in Pavia, the clinical trial *SIDIACO* (sitagliptin in diabetic patients with COVID-19). *SIDIACO* is a case–control study, in which we will compare the clinical response of diabetic patients infected by COVID-19 during a 10 days course treatment with 100 mg Sitagliptin.

Several data suggested that the latter immune pharmacological activity of DDP4 seems to be independent of its catalytic activity [35] and for this reason unaffected by the use of inhibitors of the enzymatic activity of DPP4 [36]. Other scientific evidences supported that the use of DPP4/CD26 inhibitors may act to antagonize airway inflammation [37]. DPP4 inhibition by gliptins may antagonize SARS–CoV-2 virulence and multiorgan acute and chronic damage by means of several additive mechanisms that involve: (1) reduction of cytokines overproduction [12, 30, 38, 39]; (2) downregulation of macrophages activity/function [40]; (3) enhancement of GLP-1 anti-inflammatory activity [41, 42], particularly in those aged patients

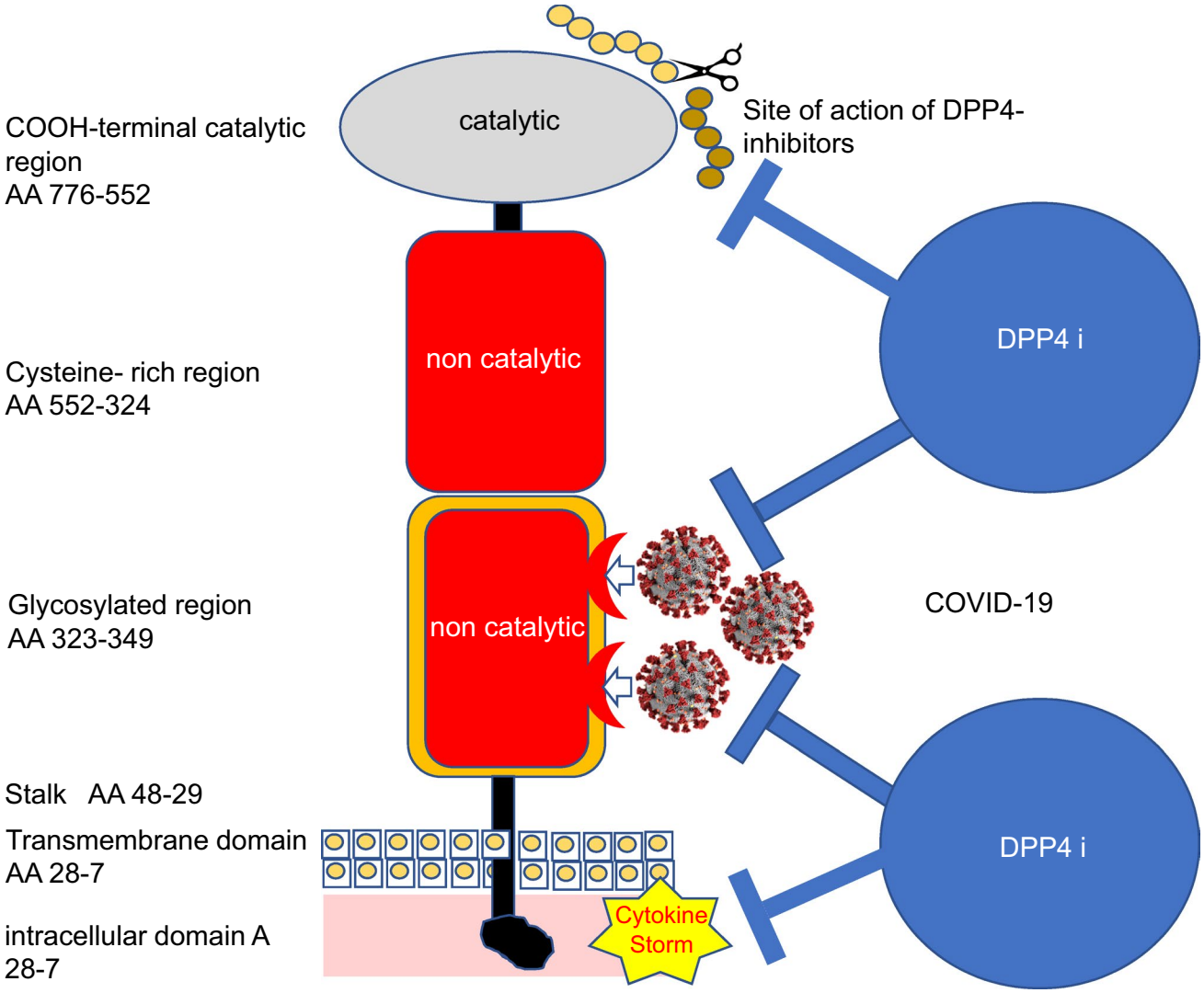

Fig. 1 Working hypothesis on the possible role of DPP4 inhibition (DPP4i) with gliptins to antagonize COVID-19 virulence and immunopathology

with COVID-19 [43]; (4) stimulation of direct pulmonary anti-inflammatory effects [44, 45].

In summary, we hypothesize (Fig. 1) that DPP4/CD26 inhibition with gliptins, and particularly with those with more highly selectivity for DPP4 [46, 47], could represent a new strategy to support the treatment of COVID-19 in patients with or without diabetes.

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Code availability Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare no present or potential conflicts of interest. This study was performed without the support or involvement of any external funding source or study sponsor in any phase of the investigation, or in the writing or submission of the manuscript.

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