Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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A potential therapeutic combination for treatment of COVID-19: Synergistic effect of DPP4 and RAAS suppression

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ABSTRACT

COVID-19, caused by the novel coronavirus SARS-CoV-2, is an abbreviated name for coronavirus disease 2019. COVID-19 became a global pandemic in early 2020. It predominantly affects not only the upper and lower respiratory tract, but also multiple organs, including the kidney, heart, and brain. The mortality of COVID-19 patients is high in men and in elderly patients with age-related diseases such as hypertension and diabetes. The angiotensin converting enzyme-2 (ACE-2), a component in the renin–angiotensin–aldosterone system (RAAS), plays as cell surface receptors for SARS-CoV-2. A recent study proved that coronavirus SARS-CoV-2 also uses dipeptidyl peptidase-4 (DPP4, also known as adenosine deaminase complexing protein 2, CD26) as a co-receptor when entering cells. In addition, DPP4 is also implicated in the regulation of the immune response. Thus, the combination of DPP4 inhibition and suppression of ACE-2/RAAS may be a novel therapeutic strategy for combating this pandemic.

Introduction

COVID-19 originally emerged in Wuhan City in the Hubei region of China, and then spread to the rest of the world [1,2]. COVID-19 is caused by the coronavirus SARS-CoV-2. It causes severe respiratory syndrome through a direct cytotoxic viral effect and severe systemic inflammation, and has a relatively high mortality rate [1,3]. Common pathological symptoms of COVID-19 include fever, dry cough, fatigue, lymphopenia, and shortness of breath [2]. Elderly people often develop severe symptoms, and the disease frequently leads to death [4].

Angiotensin-converting enzyme (ACE)-2 is a membrane-associated aminopeptidase expressed in most organs, including in lung, renal, cardiac, endothelial, and intestinal cells. It contains an N-terminal peptidase M2 domain, and a C-terminal collectrin renal amino acid transporter domain. ACE-2 functionally lowers blood pressure by catalyzing angiotensin II into the vasodilator angiotensin (1–7) [5]. In addition, ACE-2 serves as a receptor for some coronaviruses in hosts, including SARS-CoV and SARS-CoV-2. Once the spike S1 protein of SARS-CoV-2 binds to the enzymatic domain of ACE-2 on the surface of cells, endocytosis occurs, and the virus is translocated into endosomes inside cells [4,5].

Several studies have also suggested that SARS-CoV-2 may be using a co-receptor, namely the dipeptidyl peptidase-4 (DPP4) receptor (also used by MERS-Co-V) when entering the cells [3]. In particular, SARS-CoV-2 is able to infect T lymphocytes despite their very low expression level of ACE-2, implying an alternate receptor for viral entry [5,6]. DPP-4 is also known as adenosine deaminase complexing protein 2 or CD26, and is involved in various physiological processes and diseases of the immune system. DPP-4 is ubiquitously expressed in various tissues, including the lungs, kidneys, small intestine, and heart [3]. These tissues are also predominantly impaired in patients infected with COVID-19. Among elderly patients (average age: 80 years) infected with SARS-CoV-2 in Italy in early 2020, the mortality rate was highest in patients with hypertension (69%), followed by those with type 2 diabetes (31%), and those with ischemic heart diseases (27%) [5]. The same trend was observed, albeit to a lesser extent, in China, where patients with hypertension (24%), diabetes (16%), and cardiovascular abnormalities (9%) had the highest mortality rates [5,7]. These clinical data regarding the high incidence of hypertension in fatal cases suggest that the renin-angiotensin-aldosterone system (RAAS) is a critical risk factor for infection and pathogenesis of COVID-19.

Several studies have indicated that DPP4 is involved in the immune response, and this effect seems to be independent of its catalytic effects for glucagon-like peptide-1 [8,9]. In fact, DPP4 was originally identified

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as a surface marker of T lymphocytes [10]. Clinical evidence showed that patients with severe COVID-19 had increased levels of cytokines such as interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor alpha (TNF-α) [10]. T cell exhaustion by viral antigens and the aforementioned cytokines limits viral clearance via humoral immunity [11]. These increases in cytokines create a cytokine storm, further leading to significant damage to the lungs and other tissues [12]. Therefore, DPP4 inhibition may also inhibit inflammation of the airway and other organs beyond the reduction of viral infection of hosts [13].

Testing the hypothesis

We hypothesized that the suppression of DPP4 and RAAS using inhibitors and/or antibodies may be beneficial for the treatment of COVID-19, in at least two respects. One is to reduce viral entry and replication into its target organs during the early phase of infection. The second is to prevent the cytokine storm, which has anti-inflammatory effects after the middle phase of infection.

Discussion

Despite the lack of sufficient pathological data, many studies have provided important insights into the role of ACE-2/RAAS and DPP4 during viral infection. Although ACE-2 levels are increased by treatment with ACE inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs) in murine models [14,15], there is no definitive evidence to suggest that these inhibitors worsen COVID-19 [16–18]. Instead, Sanchis-Gomar et al. emphasize in their review, based on more than 59 articles, that increased ACE-2 expression does not necessarily imply an increased risk of infection or disease severity [17]. Recently, some clinical studies also found that ACE-Is and ARBs provide beneficial effects to COVID-19 patients with hypertension and even lung injury [16,19–21]. Apart from the receptor role of ACE-2 in infection, these conflicting observations indicate that RAAS might be more complex, and serve as a double-edged sword for the pathological development of COVID-19. More research on this topic is needed.

Lung failure is the predominant cause of death in COVID-19 patients, as the lungs are the first site of this respiratory virus infection. However, hypertension is the highest risk factor for mortality among elderly people infected with COVID-19. COVID-19 exploits ACE-2 as a receptor to enter host cells, and ACE-2 expression is much higher in the kidney than in the lungs [22,23]. Transmembrane protease serine 2 (TMPRSSs) is expressed in the proximal convoluted tubules of the kidney, and its proteolytic activity is essential for viral entry into target cells [24,25]. Hence, recovered COVID-19 patients have the potential to further develop severe kidney impairment in the future [26].

The clinical stage of COVID-19 consists of three phases. The first phase comprises the first days after disease onset, and is characterized by fever and coughing. Over days 8–12, there is a transition to an inflammatory phase. The symptoms of shortness of breath and hypoxia appear during this period. The last phase comprises the hyper-inflammation stage, which involves a host immune response to the viral infection, is characterized by acute respiratory distress syndrome, and frequently develops into a procoagulant state in patients [2]. Hence, different treatment methods are effective according to the progress of COVID-19, and appropriate treatments likely include administering antivirals during the early stage of the disease, and anti-inflammatory drugs from the middle to late stages.

In spite of the absence of experimental validation, Vankadari et al. modeled the homo-trimer structure of domains using SWISS-MODEL (https://swissmodel.expasy.org), and demonstrated that the S1 domain of COVID-19 spike glycoprotein may interact with human DPP4 [27]. Furthermore, recent studies showed that a humanized anti-DPP4 monoclonal antibody significantly suppressed MERS-CoV infection without altering other immune functions [28,29]. These exciting results further reinforce that the suppression of DPP4 may be useful in multifaceted ways, not only for halting the progression to the hyper-inflammatory state, but also for reducing viral infection to target cells in COVID-19 patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110186.

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