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Editorial

Aged Population and Immunocompromised Patients: Impact on SARS-CoV-2 Variants and Treatment Outcomes

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1. Introduction

Patients with an immunocompromised state are at risk of developing a long-term infection from the coronavirus 2 that causes severe acute respiratory syndrome (SARS-CoV-2). It has been shown that SARS-CoV-2 variants may emerge over the course of such chronic episodes of coronavirus disease 2019 (COVID-19) in multiple case reports [1,2]. Because a vast number of people across the world suffer from inherent or induced immunosuppression, the link between immunosuppression and the emergence of highly communicable or deadly SARS-CoV-2 variants has to be explored further and countermeasures developed [3].

Variations in the host immune response with age affect not just the capacity to fight infections, but also the capacity to construct successful vaccination defences. "Immunosenescence and inflammaging are two essential characteristics of the ageing immune system, in which the aggregation of senescent immune cells contributes to its decrease while increasing inflammatory phenotypes promote immunological malfunction" [4,5]. Within lymphoid and nonlymphoid peripheral organs, age-related alterations in the immune system influence cells and soluble components of both innate and adaptive immune responses (Figure 1). These alterations influence not just infection vulnerability, but also illness development and clinical consequences.

COVID-19 seems to show typical clinical symptoms in immunocompromised people. Cancer patients and solid-organ transplant recipients may have an increased chance of developing COVID-19 [6]. Based on present evidence, patients receiving biologics may not be at a greater risk of severe illness; nevertheless, it is unclear if they are at a reduced risk of severe COVID-19. According to Mueller AL [7], the viral replication process is favoured in aged and immunocompromised individuals due to inefficiency of the circulatory macrophages and cellular immunity. This situation allows hyperactivation of circulatory chemokines to enter systemic circulation with the activation of fibroblasts. The virus infects microvascular pericytes in other organs, and fluid fills the alveolus, limiting lung capacity. Microvasculature clotting is triggered by a cytokine storm, resulting in severe hypoxia, coagulopathy, and organ failure.

In summary, the age and immunocompromised state of the patient provides more time to SARS-CoV-2 in the host body with limited defence that ultimately leads to the viral mutations and emergence of new viral variants of SARS-CoV-2. As such, antiviral drugs and vaccinations are required to help immunocompromised patients fight against SARS-CoV-2 infection and severe COVID-19 disease.

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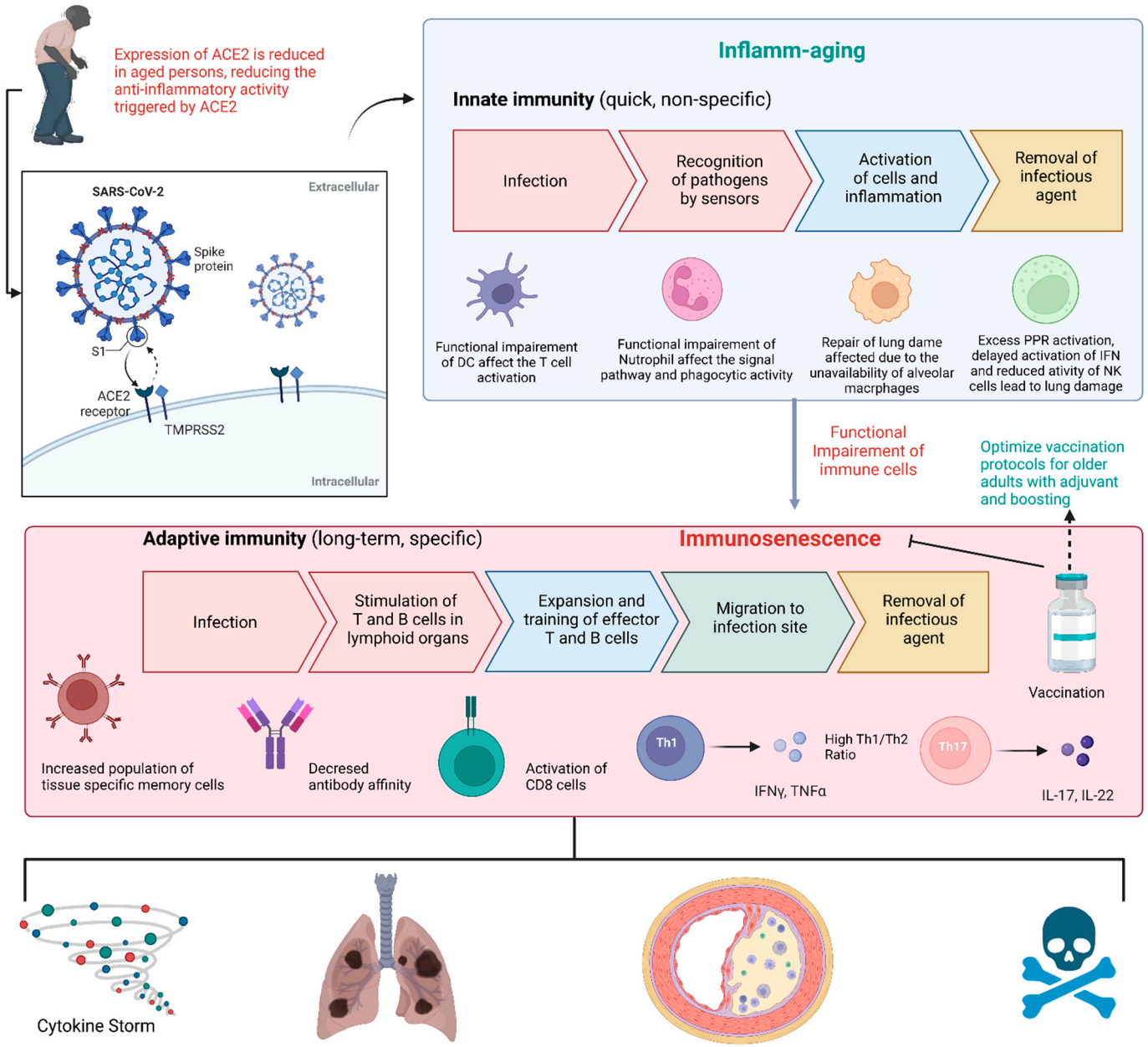

Figure 1. Alteration of the immune system in the aged population and connection with COVID-19 management.

2. Bioinformatics and Drug Repurposing

Thus far, there have been over 6.35 million deaths due to COVID-19 and almost 550 million reported cases across the globe, conceivably being the largest threat to mankind in recent years [8]. The severity and outcome of COVID-19 greatly depend on the patient's age and immunity [9]. Immunosenescence has become the emerging challenge for the aged population. Viral evolution in immunocompromised and aged patients is considered as an important factor in the emergence of viral variants [10]. Because of the change in genetic material of the virus, different variants of concern of SARS-CoV-2 have been identified during this pandemic, such as "alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), and omicron (B.1.1.529)" which are associated with enhanced transmissibility and increase virulence [11–17]. In addition, omicron has diverged into sublineages "BA.1

(B.1.1.529.1), BA.2 (B.1.1.529.2) and BA.3 (B.1.1.529.3), and more recently, BA.4 and BA.5" have emerged, each having additional mutations to the spike protein and increased growth rate [18]. The development of variants is due to mutations in the virus spike protein in order to escape from the host immune system or to increase infectivity. The primary targets for most therapeutic methods against SARS-CoV-2 are against the spike protein and the receptor-binding domain (RBD), which alter the binding to the host cell receptor angiotensin-converting enzyme 2 (ACE2) [19–27]. Adding to this complexity, more recently, it has been shown that SARS-CoV-2 can enter host cells via additional receptors [28]. At present, there are no efficacious antiviral drugs available for COVID-19 treatment even though a number of antivirals are being used in moderate–severe disease individuals, those at high risk and the immunocompromised, such as remdesivir [29], with a number showing promise as antivirals [30]. However, Ritonavir-Boosted Nirmatrelvir (Paxlovid) that is in current use in the US and elsewhere, and has been shown to be effective in treating disease and preventing hospitalization if administered within 5 days of the onset of symptoms [31]. In spite of the fact that coronaviruses have undergone notable genetic evolution, they still have remarkable similarities, which should be the basis for the identification of promising targets for antiviral therapies to combat the pandemic.

Since the advent of the COVID-19 pandemic, the application of bioinformatics and drug repurposing has accelerated the research efforts for COVID-19 drug discovery. Different chembioinformatic approaches (fragment-based, structure-based, and ligand-based modelling strategies), and immunobioinformatics may be useful hall markers to prioritize the drug candidate and vaccine candidate, respectively, for further experiments [32–34]. Computational drug repurposing (repositioning) is an effective approach to identifying novel drug-target interactions using the drugs already known to be safe, which provides the advantages of significantly reducing the time for drug development and reduced failure rate [35]. This approach typically includes a virtual screening of drug libraries to find suitable drug–target pairs using molecular-shape similarity methods and molecular docking and binding free energy calculations to predict binding affinity. Numerous monoclonal antibody (mAb)-based treatments with repurposed mAbs and novel SARS-CoV-2-specific mAbs are available for COVID-19 management [36]. In addition, nano-based drug delivery systems can be applied for efficient targeted delivery [37–41].

3. Impact of Vaccines

Within 6 months of the global pandemic, millions of cases surged with many hospitalizations and deaths, in particular to the elderly and those with underlying secondary disease and weak immune systems. As a consequence, this added much strain to the health care system as well as the global economic status suffering huge losses, primarily in tourism, aviation, entertainment, sports, retail and hospitality due to COVID-19 restrictions. Many suffered social and psychological issues including the aged, children, students and health workers. As quickly as the pandemic came upon us, so did world-wide efforts to develop effective vaccines against SARS-CoV-2 virus. Several vaccines were approved as emergency-use rollouts around the world and numerous are in preclinical and in human clinical trials. A number of vaccine platforms have been used with the aim to deliver viral constituents or fragments of the virus to immune cells, to stimulate antibody and/or T cell responses. As of June 2022, the WHO documented 147 vaccines in clinical development and 195 vaccines in the preclinical development stage for COVID-19. Some of the platforms used include live attenuated or whole inactivated virus as have been in traditional vaccines, viral-vectors, small virus-like particles, mRNA, DNA, proteins, peptides and DC-based vaccines [42].

Vaccination aims to prevent disease or transmission in the community. With world-wide mass vaccinations, COVID-19 disease can be controlled, by preventing hospitalizations, severe disease and death. The Pfizer-BioNTech, Moderna and Johnson & Johnson vaccines have been authorized by the Food and Drug Administration (FDA, USA) and especially the immunocompromised and elderly have been advised to receive booster

injections. In fact, in a study of 780,225 veterans in the Veterans Health Administration covering 2.7% of the US population, vaccination protected against death in those infected against the delta variant. In those aged <65years, vaccination decreased death by 73% (Johnson & Johnson), 81.5% (Moderna) and 84.3% (Pfizer-BioNTech), and for those above 65 years, protection was 52.2%, 75.5% and 70.1%, respectively [43]. In the UK, the Oxford-AstraZeneca vaccine offered 91% effectiveness (in 115,000 people) in preventing death in those who were double-vaccinated and had subsequently tested positive for the delta variant [44].

Like most vaccines, there are reports that vaccination against SARS-CoV-2 can cause, in some cases, pain at the injection site, fever, fatigue, and headache. Other reported effects include decreased haemoglobin levels, increased bilirubin levels, altered serum glutamic-oxaloacetic transaminase and serum glutamic pyruvic transaminase [45,46], edema [47], erythema [48], myocarditis [49], thrombosis, and thrombocytopenia [50]. Several clinical trials are being conducted in order to assess the safety profile of different COVID-19 vaccine platforms. Overall, despite the rare adverse reactions reported, vaccination protects against hospitalizations and deaths, even in breakthrough cases.

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