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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The mechanism behind flaring/triggering of autoimmunity disorders associated with COVID-19

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Dear Editor,

Based on the study by Perrot and co-workers on the ACPA-positive rheumatoid arthritis after SARS-CoV-2 infection [1], we should aim at understanding the mechanisms behind autoimmunity related to COVID-19 pathophysiology. As you know, recent studies have shown that some COVID-19 patients showed the dramatically increased reactivity of their autoantibodies against many human autoantigens, such as several immunomodulatory extracellular and secreted proteins, including surface proteins, chemokines, complement components, and cytokines [2]. This posed important questions on how and why such autoantibodies were elicited. The most obvious explanation is comorbidity, where SARS-CoV-2 infected patients with the autoimmune diseases (AIDs), suggesting an association between AIDs and an increased risk of SARS-CoV-2 infection and even higher severity of COVID-19. Although the capability of SARS-CoV-2 to efficiently infect AID patients has been thoroughly investigated, it is still unclear whether SARS-CoV-2 infections are associated with the remittance or relapse/flare-up of AIDs [3,4]. Alternatively, the autoantibodies can appear after SARS-CoV-2 infection of non-AIDs individuals, raising another fundamental question: how the formation of autoantibodies is triggered then? Of note, several viruses, such as coxsackie B virus, rotavirus, influenza A virus, herpes virus, measles virus, mumps virus, rubella virus, and SARS-CoV-2 have been proposed to modulate the induction and development of AIDs [5,6]. (See Fig. 1.)

Several mechanisms have been suggested by which SARS-CoV-2 and other viruses can induce autoimmune responses in infected patients (Figure 1). These include molecular mimicry, epitope spreading, bystander activation, presentation of cryptic antigens, B-cell polyclonal activation, the existence of the viral and/or bacterial superantigens [7,8] and the post-translational modifications (PTMs, such as the citrullination). One of the consequences of the SARS-CoV-2 infection is cellular damage in various tissues, resulting in release of intracellular constituents, such as cell-free DNA and peptidylarginine deiminase enzymes (PADs) into an extracellular milieu [9]. In several AIDs, PADs-catalyzed deamination of arginine residues generates citrullinated proteins and peptides (e.g., cyclic citrullinated peptide, CCPs) that serves as targets for creation of specific autoantibodies [10].

SARS-CoV-2 infection was shown to trigger the onset of two systemic AIDs (i.e., Systemic Lupus Erythematosus (SLU) [1] and Rheumatic Arthritis (RA) [11]) with circulating anti-CCP2, anti-CCP3, anti-PAD2, and anti-PAD4 autoantibodies found during and after SARS-CoV-2 infection. These observations suggested that CCPs are not solely responsible for this mechanism, as the humoral and cellular immunity was detected against PADs [1]. This is in line with previous observations, where anti-PAD4 antibodies were detected in 30-50% of established RA patients, and in 20% of patients with positive anti-CCP, anti-PAD4 were detected as well [12]. Furthermore, anti-PAD3 (that can cross-react with PAD4) were detected in 10-20% of RA patients [13], whereas anti-PAD2 antibodies have been identified in patients with less severe RA, associated with moderate swelling joints [14]. These autoantibodies might modulate catalytic activities of PADs. Furthermore, auto-citrullination (self-post-translational modification) of PADs enzymes could not be avoided during SARS-CoV-2 infection, specifically during the exponential increase in infection manifestation and disturbance of the Ca^{2+} balance, which is crucial for PADs catalysis.

In line with these considerations are the results of the bioinformatics analysis of the multi-omics datasets (RA, amyotrophic lateral sclerosis (ALS), and COVID-19) that was conducted via search for the four biomarkers (AGBL2/CCP2, AGBL3/CCP3, PADI2/PAD2, and PADI4/PAD4) to understand how the systemic AIDs can be triggered by SARS-CoV-2. This analysis revealed the presence of the anti-CCP2, anti-CCP3, and anti-PAD2, anti-PAD4 biomarkers in all these cases. Furthermore, since APP, TP53, TP63, and PADI3 were associated with RA+COVID, and since TP53 and TP63 were associated with RA+ALS+COVID, one can conclude that the TP53- and TP63-related pathways may be associated with COVID-related AIDs that produce anti-CCPs and anti-PADs. Although the study by Perrot and co-authors [1] answered some of the main questions and gave support for the notion that SARS-CoV-2 triggers autoimmune diseases and specifically RA, further analysis of the same serum sample for antibodies against native PADs, citrullinated PADs, and CCPs is necessary, which will further confirm the phenomenon of COVD-19 autoimmunity.

Finally, one more important point should be indicated here. Tobacco

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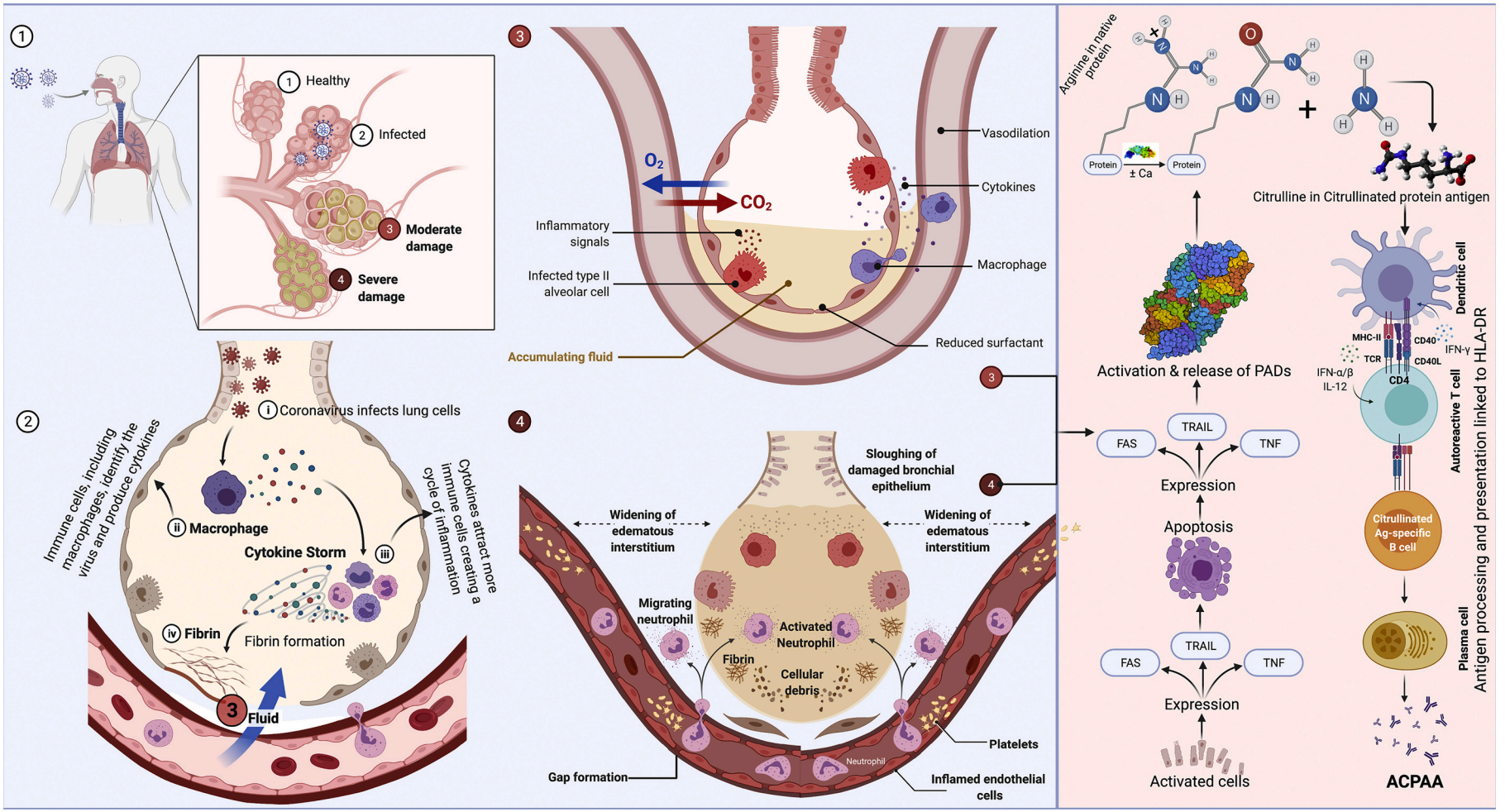

Fig. 1. The suggested scenarios behind how SARS-CoV-2 triggers autoimmune diseases. 1: Healthy 2: Infected 3: Moderate Damage (Accumulating fluid, reduced gas exchange) 4: Severe damage (Build-up of protein-rich fluid, very limited gas exchange), during moderate to severe (3-4) many cells type expects to damaged releasing their enzymatic molecules which may work on several extracellular matrices proteome creating neo-autoantigen which subsequently elicit the autoimmune response associate with the SARS-CoV-2 infection.

smoking is considered as one of the factors increasing severity of COVID-19 that can aggravate the condition of patients with COVID-19 [15,16]. In part, this is due to the ability of nicotine to activate the nicotinic receptors resulting in the enhanced apoptosis, inflammatory signaling, and protease activation via the renin-angiotensin system (RAS) and angiotensin-converting enzyme 2 (ACE2) pathways, which are used by the SARS-CoV-2 to enter the host cells [17]. Furthermore, in addition to enhancing expression of ACE2 and transmembrane serine protease 2 (TMPRSS2) and inducing a cytokine storm [17], smoking might also induce airway inflammation by triggering protein citrullination through up-regulation of PAD2 [18]. In particular, smoking increases levels of the citrullinated vimentin in lung tissue and induces the secretion of citrullinated vimentin in an Akt1- and PAD2-dependent manner [19]. This is an important observation, since citrullinated vimentin was shown to serve as one of the damage-associated molecular pattern molecules (DAMPs) acting as ligands of the toll-like receptors (TLRs) and was linked to the pathogenesis of various maladies with autoimmune etiology, such as liver fibrosis, RA, and interstitial lung disease associated with RA (RA-ILD). Therefore, smoking can be an additional contributing factor to the SARS-CoV-2-flared autoimmunity disorders.

Spike protein could trigger inflammation response through the Factor H interaction of the complementary alternative pathway and mannose-binding lectin (MBL) interaction of the complementary lectin pathway which has been associated with the COVID-19 patients with fatality [20]. In summary, these observations should focus our attention on COVID-19 patients genetically predisposed for autoimmune and/or autoinflammatory disorder and carefully monitor them during mass vaccinations against COVID-19 with a vaccine dependent on spike glycoprotein antigens. Obviously, the proposed here model is one autoimmune mechanism among many.

Ethical approval information

Non applicable.

Data sharing statement

There are no data in this work (letter to the Editor).

Contributorship

All the authors gave substantial contributions to the conception or design of the work, acquisition, analysis or interpretation of data, drafting the work or revising it critically for important intellectual content and final approval of the version published.

Declaration of Competing Interest

There are no competing interests for any author.

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