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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Autoimmunity to ACE2 as a possible cause of tissue inflammation in Covid-19

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A B S T R A C T

Hypothesis: The delayed lung damage after SARS-CoV-2 infection may be caused by an autoimmune response to ACE2 induced by forced presentation of the ACE2 protein in a complex with CoV Spike in Fc Receptor positive Antigen Presenting Cells in the lung. The likelihood that this hypothesis is valid is ***low***, but it is easily tested.

Testable predictions: 1) Autoantibodies and T cells to ACE2 may be found in patients with the lung damage but not in those without 2) There may be an HLA linkage with the delayed lung disease 3) Vaccines based on the spike protein might initiate the process by amplifying Fc mediated uptake of ACE2-Spike complexes into APCs.

Practical implications: The development of autoantibodies to ACE2 might predict the development of the inflammatory phase of Covid-19 disease. It might be wise to consider engineering versions of the spike that no longer bind to ACE2 for inclusion in vaccines.

Background

Infection by SARS-CoV-2 is followed by an inflammatory pneumonia in ~14% of cases [1] and widespread organ damage [2]. The risk increases with age and certain predisposing conditions. Of these, hypertension stands out with 6.3% risk of death [3]. The virus enters cells by binding to the ACE2 protein [4]. ACE2 expression may be increased in hypertension, and this could be the basis for the predisposition by enhancing uptake of virus into cells that express ACE2 in lung, heart, blood vessels and kidney [5].

The pathological basis for the onset of inflammatory pneumonia, after initial recovery and even clearance of the virus, is not known. A similar inflammatory pneumonia associated with SARS vaccination, or re-exposure, was thought to be due to an overgrowth of T cells [6,7], and can be transferred by antibody specific for Spike protein in an NHP model [8]. In several animal models vaccination with full length spike predisposed to the inflammatory lung disease [6]. For SARS the inflammatory pneumonia was associated with an early high titre neutralising antibody response in patients [9], and severe Covid-19 disease is also associated with higher antibody titres [10]. The role of antibody in pathogenesis may be to concentrate the Spike protein in Fc Receptor bearing Antigen Presenting Cells in the lung. But why the spike protein should initiate such a damaging immune response is not known. The specificity of the T cells damaging the lung is also not known.

The hypothesis

The interaction between ACE2 and the Receptor Binding Domain of the Spike protein is high affinity (~10 nM), equivalent to many monoclonal antibodies [4]. As such, the association of ACE2 with the Spike protein is likely to be long lived, and is expected to result in ACE2 entering antigen presenting cells associated with the Spike protein on viral particles or vaccines. This may be enhanced by Fc mediated uptake via Fc Receptors once an antibody response to the spike has occurred, and may set up conditions for intense presentation of ACE2 epitopes to T and B cells, aided by strong T cell help from epitopes derived from the attached Spike or other viral proteins. This may be enough to break self-tolerance to ACE2.

In principle, there may be protean downstream effects of an autoimmune response to ACE2. ACE2 expression in lung, heart and kidney would lead to inflammation at those sites. In addition, loss of local ACE2 activity may be associated with increased activity of angiotensin II through the AT2 type I receptors in the lung, that are thought to be involved in initiating inflammation [11]. Reduced ACE2 activity has been linked to increased thrombosis [12], and a thrombotic tendency has been described in severe Covid-19 disease [13]. Autoantibodies to ACE2 have been described [14] associated with vasculopathies including pulmonary hypertension.

Last word

All of this is highly speculative, but the basic idea is testable by looking for antibodies and T cell responses to ACE2 in patients with severe disease. *"Hypotheses come into our laboratories in armfuls, they fill our registers with projected experiments, they stimulate us to research - and that is all."* [15]. Note added in proof: an independant, but similar,

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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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