

Targeted COVID-19 therapy: What can we learn from autoimmune kidney diseases?

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Various viruses and bacteria have long been known to cause autoimmune diseases where there is such a predisposition. This phenomenon also seems to play a major role in SARS-CoV-2, especially in severe courses. The body's own immune cells are activated, with the formation of autoantibodies that attack the body's own healthy cell structures (proteins, autoantigens); deposits of immune complexes can then trigger

severe inflammatory processes and cell destruction in the body.

Some nephrological diseases are likewise of autoimmunological etiology, one example being [systemic lupus erythematosus](#) (SLE), a chronic, mostly relapsing-remitting inflammatory [disease](#) with life-threatening courses in some cases. Manifestations occur on the skin and in organs such as the lungs, heart, CNS, muscles/joints—and the kidneys. Lupus nephritis (kidney inflammation) occurs in almost three out of four cases and determines the outcomes of SLE. Many SLE patients are therefore treated or co-managed by nephrologists, with the aim of avoiding chronic kidney disease and the necessity for chronic dialysis treatment. The causes of SLE are multifactorial (e.g. genetic predisposition, hormonal and environmental triggers). In SLE, antiphospholipid antibodies (aPLs; i.e., autoantibodies against phospholipid-binding proteins) are often found, but also in other autoimmune diseases of the vascular system presenting variable clinical pictures. aPLs can interfere with the clotting system, so there is usually a tendency to thrombosis, and severe complications in pregnancy are also possible in affected women.

More and more similarities between severe COVID-19 and SLE or autoimmune diseases have meanwhile been described. An increase in autoantibody-forming lymphocytes (B cells) and their activation are also observed in critically ill COVID-19 patients, as in acute SLE relapses. aPLs have also been detected in COVID-19 patients, and aPL concentrations correlated with the severity of the disease. There are also some interesting clinical parallels: A pioneering study from Germany shows that early kidney involvement (proteinuria, hematuria) can determine outcomes in COVID-19 patients—as is the case with SLE.

A new study on the subject has now been published by the working group led by Prof. Wolfram Ruf, Mainz, in the renowned journal *Science*. The study showed for the first time that [antiphospholipid](#)

[antibodies](#) bind to the EPCR LBPA complex. This molecule complex is located at the biochemical interface of the innate immune or pathogen defense system and the clotting system. It is a lipid-protein receptor complex consisting of endosomal LBPA (lysobisphosphatidic acid from endosomes) and the EPC (endothelial protein C) receptor located on the interior surface (endothelium) of the blood vessels. In this complex, the EPC receptor presents LBPA as a pathogenic cell surface antigen. aPL binding to the EPCR-LBPA complex then activates both the endosomal inflammatory pathway and the coagulation cascade. This leads to interferon production in immune cells and to a special expansion of B cells, which then produce further autoantibodies in a self-reinforcing autoimmune signaling loop. With regard to therapy, the study also showed that, in the lupus mouse model, the specific pharmacological blockade of this EPCR-LBPA signaling inhibited severe aPL-related damage.

"Even if the pathogenic mechanism and significance of autoantibody formation in COVID-19 are not yet fully understood, it is possible that the autoimmune response, once triggered, could be the real cause of many severe COVID-19 courses," commented Prof. Dr. Julia Weinmann-Menke, Mainz, the DGfN Press Officer, at the Opening Press Conference of the ERA-EDTA Congress. She and her colleagues at the universities of Mainz, Greifswald (Prof. Dr. Jens Fielitz) and Berlin are therefore planning a cooperative clinical research project to further investigate this autoimmune disease and to find new approaches for immunological COVID-19 therapies. "Our project is based on the hypothesis that an infection-associated autoimmune response by autoantibodies is implicated in many cases of organ damage in patients with severe COVID-19," explains Prof. Weinmann-Menke. The study aims to establish a high-throughput test procedure (multiplex assay) that can be used to identify specific immune responses (immunoproteomics) to autoantigens (especially against cerebral, cardiac and renal proteins) that occur in COVID-19. Autoantibody-forming memory B cells, and

the specificity of autoantibodies (tissue specificity and cross-reactivity with other organs) are to be analyzed by conducting in vitro tests. The glycosylation of autoantibodies, which is known to enhance their effect in many cases, is also to be investigated.

"Immunomodulatory therapies used or being tested in the treatment of nephrological [autoimmune diseases](#) such as SLE may also be successful in severe COVID-19 courses," concludes Prof. Weinmann-Menke. "We hope that new diagnostic options for patients will provide us with better risk assessment and more targeted therapeutic approaches, also for non-COVID-associated immune phenomena."

More information: [1] Müller-Calleja N, Hollerbach A, Royce J et al. Lipid presentation by the protein C receptor links coagulation with autoimmunity. *Science* 2021 Mar 12; 371 (6534): eabc0956. [DOI: 10.1126/science.abc0956](#)

[2] Woodruff MC, Ramonell RP, Nguyen DC et al. Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19. *Nature Immunology*, 2020; [DOI: 10.1038/s41590-020-00814-z](#).

www.nature.com/articles/s41590-020-00814-z

[3] Gross O, Moerer O, Weber M et al. COVID-19-associated nephritis: early warning for disease severity and complications? *The Lancet* 2020. Published: May 06, 2020. DOI:

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