References

1 Naymagon L, Berwick S, Kessler A, Lancman G, Gidwani U, Troy K. The emergence of methemoglobinemia amidst the COVID-19 pandemic. *Am J Hematol* 2020; **95**: E196–E197.
2 David SR, Sawal NS, Bin Hamzah MNS, Rajabalaya R. The blood blues: a review on methemoglobinemia. *J Pharmacol Pharmacother* 2018; **9**: 1–5.
3 Pathania V, Shankar P, Sinha P, Tripathy D. A curious case of palpitation in a leprosy patient with low grade methemoglobinemia. *Indian J Drugs Dermatol* 2018; **4**: 79.
4 Sahu KK, Mishra AK. Role of ascorbic acid in dapsone induced methemoglobinemia. *Clin Exp Emerg Med* 2019; **6**: 91–92.
5 Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of 'happy' hypoxemia in COVID-19. *Respir Res* 2020; **21**: 198.

DOI: 10.1111/jdv.17394

Autoantibodies in Covid-19 – a model for viral induced autoimmunity

Dear Editor,

The novel Coronavirus SARS-CoV-2 is suspected of acting as a trigger for autoimmune diseases and the production of autoantibodies. Retinoic acid-inducible gene (RIG)-I-like receptors (RLR), including melanoma differentiation-associated protein 5 (MDA5) and RIG-I, recognize the double-strand (ds) virus RNA and induce the production of Type I interferon (Type I IFN) as well as pro-inflammatory cytokines like Interleukin (IL)-6[1] (Fig. 1). High IL-6 levels are associated with the induction of pro-inflammatory cytokines ("cytokine storm") and development of respiratory failure.[2] On the other hand, chronically high levels of Type I IFN are related to several autoimmune diseases such as systemic Lupus erythematodes (SLE), Sjögren Syndrom, systemic sclerosis, inflammatory myopathies and rheumatoid arthritis (RA). In terms of clinical presentation and biomarkers, many similarities can be found between Covid-19 and anti-MDA5 positive dermatomyositis.[2] Moreover, allelic variations within IFN-pathway-genes can be found in those autoimmune diseases.[3] The first cases of new autoimmune phenomena related to Covid-19 were found with some delay after the outbreak of the pandemic. With a new awareness for possible induction of autoimmune-mediated phenomena associated with SARS-CoV-2 infection, the topic gained attention. In recent years, the potential role of viruses in the pathogenesis of autoimmune diseases, e.g. Epstein-Barr-Virus, has been published.[4] There have also been reports of post-vaccination onset of autoimmune diseases, most recently following SARS-CoV2 vaccination.[5] Therefore, it stands to reason to consider SARS-CoV-2 as a trigger for autoimmune phenomena. We performed a meta-analysis of recently published articles on autoimmune phenomena associated with concomitant SARS-CoV-2 infection.[6–10] Table 1 shows reported autoantibodies, increased levels of IL-6 as well as frequently reported clinical symptoms.

Several authors reported an increased frequency of at least nine autoantibodies in patients with Covid-19, with Lupus Anticoagulant (LA) being the most common (75 out of 107 patients).

LA is associated with prolonged activated partial thromboplastin time (aPTT), arterial or venous thrombosis, and in consequence cardiovascular events. Besides LA, anticardiolipin- and anti-β_2-glycoprotein-I antibodies are numbered among the group of antiphospholipid antibodies and were found in three more cases. Congruent to these findings, Covid-19 patients often showed clinical signs of coagulopathies such as hypercoagulation and thromboembolic events including pulmonary embolism and stroke.[11,12] Microangiopathic changes were represented by chilblain-like skin lesions and eruptive cherry-angioma.[13] Kolivars *et al.* hypothesized that chilblain-like lesions and microangiopathic changes are due to immunologic reactions to the viral infection. In this case, the Type I IFN response most likely happens to be early and strong in young patients resulting in microangiopathy and chilblains, overall with a short and indolent course of the infection, whereas older patients react late and inadequately to Type I IFN, which results in hypercytokinemia, hypercoagulation, and thus with an increased morbidity and mortality.[14]

A potential reason for the significantly lower rate of six out of nine mentioned autoantibodies could be their delayed presence compared to LA and anticardiolipin IgA antibodies. Furthermore, severe and acute coagulopathies need rapid investigation, due to their ability to evoke an acute life-threatening situation. Therefore, most hospitals have implemented diagnostic algorithms. In contrast, autoantibody-screenings are not part of these routine work-ups. They are time consuming and are usually done posthoc. Additionally, in most cases patients' basal autoantibody levels are not available, making it difficult to give a clear statement regarding the coherence of autoimmune phenomena and antibodies with a SARS-CoV-2 infection. In our opinion, a correlation between a SARS-CoV-2 infection and autoimmune phenomena is likely, and we propose to consider autoantibody screenings more often in diagnostic procedures, keeping autoimmune phenomena as a differential diagnosis in mind. Further studies are needed for a more founded statement on/better understanding of the coherence of the appearance of autoantibodies following SARS-CoV-2 infection.

Conflicts of interest

JB declares to have no conflict of interest. SV declares to have no conflict of interest.

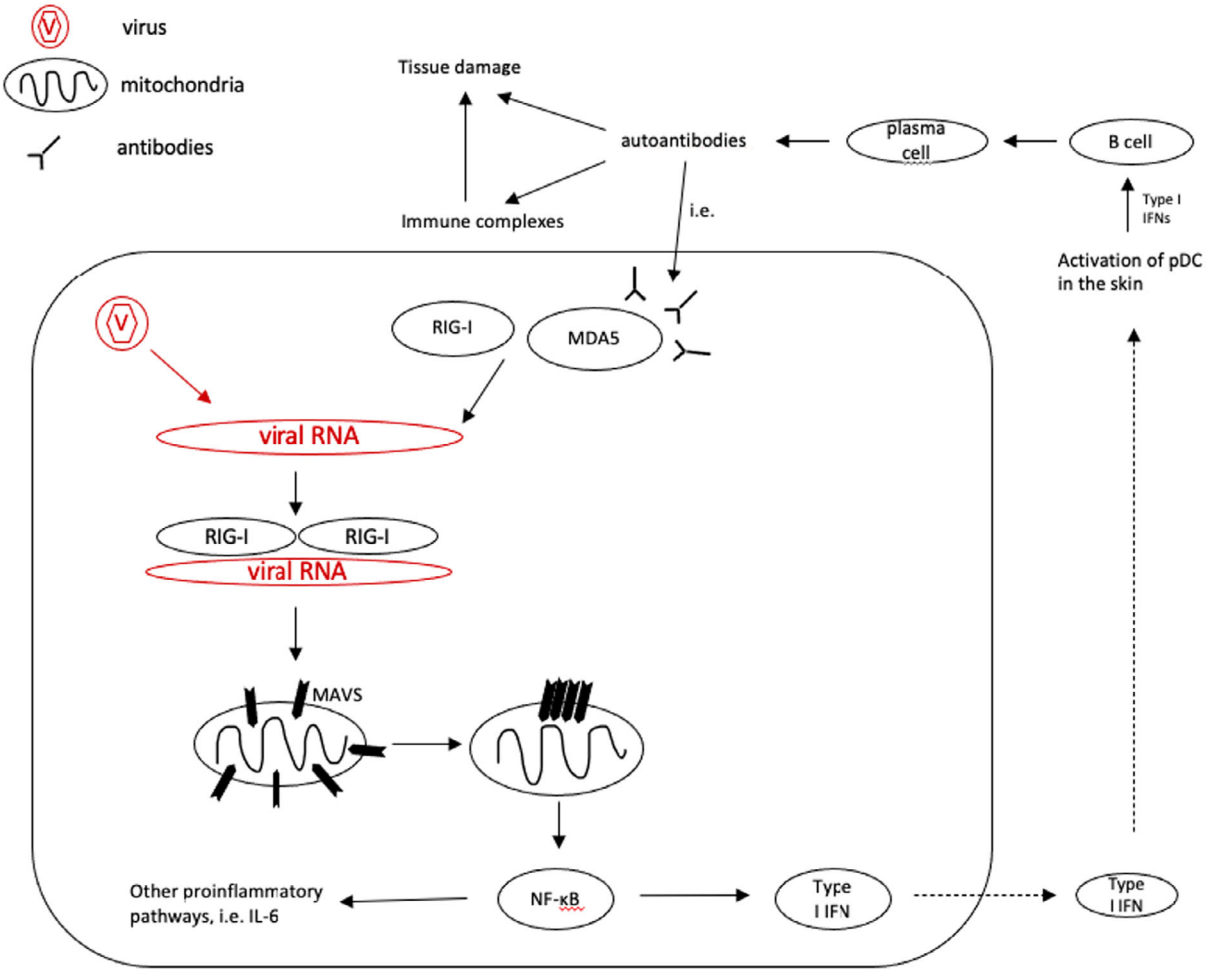

Figure 1 Retinoic acid-inducible gene (RIG)-I-like receptors (RLR), including melanoma differentiation-associated protein 5 (MDA5) and RIG-I, recognize the double-strand (ds) virus RNA and induce the production of Type I interferon (Type I IFN) and pro-inflammatory cytokines,[1] which are associated with autoimmune diseases, such as systemic Lupus erythematodes (SLE) and Dermatomyositis. After binding to the viral dsRNA, N-terminal caspase activation and recruitment domains (CARDs) of RLR interact with mitochondrial antiviral-signalling protein (MAVS) and eventually, prion-like aggregates are formed. These aggregates activate transcription factor NF-κB, which in turn stimulates the production of Type I IFN, interleukin-6 (IL-6) and further pro-inflammatory cytokines.[15] Activation of plasmacytoid dendritic cells (pDC) follows Type I IFN-mediated activation of B cells which can lead to autoantibody production, e.g, anti-MDA5 antibodies.

Funding source

No funding sources to declare.

J. Berger, S. Volc*

Department of Dermatology, Eberhard-Karls-University Tuebingen, Tuebingen, Germany

*Correspondence: S. Volc. E-mail: sebastian.volc@med.uni-tuebingen.de

References

1 Theofilopoulos AN, Kono DH, Baccala R. The multiple pathways to autoimmunity. *Nat Immunol* 2017; **18**: 716–724.

2 De Lorenzis E, Natalello G, Gigante L, Verardi L, Bosello SL, Gremese E. What can we learn from rapidly progressive interstitial lung disease related to anti-MDA5 dermatomyositis in the management of COVID-19? *Autoimmun Rev* 2020; **19**: 102666.

3 Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. *Nat Rev Immunol* 2014; **14**: 36–49.

4 Steed AL, Stappenbeck TS. Role of viruses and bacteria-virus interactions in autoimmunity. *Curr Opin Immunol* 2014; **31**: 102–107.

5 Gambichler T, Scholl L, Dickel H, Ocker L, Stranzenbach R. Prompt onset of Rowell's syndrome following the first BNT162b2 SARS-CoV-2 vaccination. *J Eur Acad Dermatol Venereol* 2021; **35**: e415–e416.

6 Ehrenfeld M, Tincani A, Andreoli L *et al*. Covid-19 and autoimmunity. *Autoimmun Rev* 2020; **19**: 102597.

Table 1 Overview of reported autoantibodies in articles included in meta-analysis.[6–10]

	Number of patients
Autoantibodies	**108**
Lupus anticoagulant	75
Anti-nuclear antibodies	10
Anti-erythrocyte antibodies	7
anti-60 kDa SSA/Ro antibodies	5
anti-52 kDa SSA/Ro antibodies	4
Anti-cardiolipin IgA + anti-β_2-glycoprotein I IgA und IgG	4
anti-GD1b-IgG	2
Anti-ADAMTS-13 antibodies	1
Other laboratory findings	**51**
IL6 ↑	51
Clinical symptoms	**143**
Chilblain-like lesions	43
Pulmonary embolism	25
Stroke	11
Exanthema	4
Thrombosis of the extremities	3
Coagulopathy	3
Chickenpox-like vesicles	2
Eruptive cherry angioma	1

Other laboratory findings included an increased IL-6.[16] Moreover, a summary of frequent clinical symptoms observed in the context of SARS-CoV-2 infection and not attributable to the infection itself.[6,11–14]

7 Lazarian G, Quinquenel A, Bellal M *et al*. Autoimmune haemolytic anaemia associated with COVID-19 infection. *Br J Haematol* 2020; **190**: 29–31.
8 Albiol N, Awol R, Martino R. Autoimmune thrombotic thrombocytopenic purpura (TTP) associated with COVID-19. *Ann Hematol* 2020; **99**: 1673–1674.
9 Zhou Y, Han T, Chen J *et al*. Clinical and autoimmune characteristics of severe and critical cases of COVID-19. *Clin Transl Sci* 2020; **13**: 1077–1086.
10 Dalakas MC. Guillain-Barré syndrome: The first documented COVID-19–triggered autoimmune neurologic disease. More to come with myositis in the offing. *Neurol Neuroimmunol Neuroinflamm* 2020; **7**: e781.
11 Klok FA, Kruip M, van der Meer NJM *et al*. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020; **191**: 145–147.
12 Oxley TJ, Mocco J, Majidi S *et al*. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med* 2020; **382**: e60.
13 Bouaziz J, Duong T, Jachiet M *et al*. Vascular skin symptoms in COVID-19: a french observational study. *J Eur Acad Dermatol Venereol* 2020; **34**: e451–e452.
14 Kolivras A, Dehavay F, Delplace D *et al*. Coronavirus (COVID-19) infection-induced chilblains: A case report with histopathologic findings. *JAAD Case Rep* 2020; **6**: 489–492.
15 Hou F, Sun L, Zheng H, Skaug B, Jiang Q-X, Chen ZJ. MAVS forms functional prion-like aggregates to activate and propagate antiviral innate immune response. *Cell* 2011; **146**: 448–461.
16 Chen N, Zhou M, Dong X *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; **395**: 507–513.

DOI: 10.1111/jdv.17396

LETTERS TO THE EDITOR

Increase in early syphilis diagnoses in the young heterosexual population of Reunion Island: surveillance data, 2010–2018

Editor

Since the early 2000s, the number of syphilis cases in France has been growing, affecting mainly men who have sex with men (MSM).[1,2] In Reunion Island, a French department located in the Indian Ocean, a resurgence of the disease has been observed since 2006 and cases of congenital syphilis have been reported since 2008.[3,4]

ResIST, a sexually transmitted infection (STI) surveillance network based on the voluntary participation of clinicians working in STI clinics, has been described before.[1] In Reunion Island, the three STI clinics have been participating since 2010. Analysis of 2010–2018 surveillance data aimed to describe the trend of the number of early syphilis diagnoses and to compare the clinical and sociodemographic characteristics between Reunionese patients and those in mainland France (excluding Ile-de-France where specific epidemiological pattern is observed).

Between 2010 and 2018, the number of early syphilis diagnoses reported in Reunion Island increased by a factor of 4 (37 to 161 diagnoses). The characteristics of patients diagnosed with early syphilis in Reunion Island and mainland France are presented in Table 1. In 2018, in Reunion Island, 30% of reported cases were in women, of whom 27% were pregnant, 22% in heterosexual men and 47% in MSM, compared to 5%, 8% and 83%, respectively, in mainland France. In 2018, patients in Reunion Island were significantly younger than in mainland France. In Reunion Island, over the 2010–2018 period, women were younger than men (Fig. 1) and the median age of infected heterosexual women decreased from 33 years in 2014 to 22 years in 2018.

The proportions of primary and secondary forms increased in Reunion Island between 2010 and 2018 regardless of sexual orientation and were higher in heterosexual men and MSM than in heterosexual women throughout the study period. In 2018, in Reunion Island, 25% of patients presented a HIV coinfection and 25% another STI coinfection.

Four factors could likely explain the rise in the number of early syphilis diagnoses in Reunion Island: (i) an actual increase in the number of cases, as suggested by the increase in the proportions of primary and secondary forms of the disease; (ii) an increase in screening coverage; (iii) a shift in patient visits from private medicine to STI clinics; (iv) improvements in ResIST surveillance.