Rīgas Stradiņa universitāte

SARS-CoV-2 un autoimunitāte

Paradigma vai novitāte

Lība Sokolovska
RSU Mikrobioloģijas un Virusoloģijas institūts

AUTOIMUNITĀTE - imūnā atbilde pret paša antigēniem

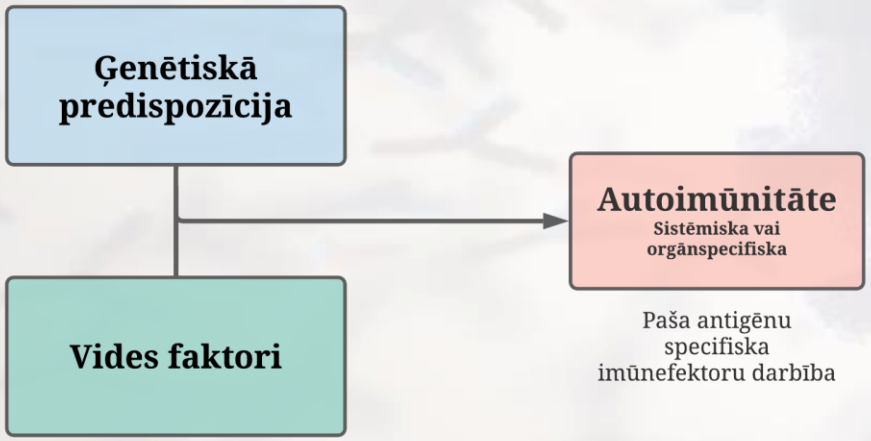


TABLE 15-2 Association of HLA Alleles with Autoimmune Disease

Disease	HLA Allele	Odds Ratio[1]
Rheumatoid arthritis (anti-CCP Ab positive)[2]	*DRB1, 1 SE* allele[3]	4
	DRB1, 2 SE alleles	12
Type 1 diabetes	*DRB1*0301-DQA1*0501-DQB1*0201* haplotype	4
	*DRB1*0401-DQA1*0301-DQB1*0302* haplotype	8
	*DRB1*0301/0401* heterozygotes	35
Multiple sclerosis	*DRB1*1501*	3
Systemic lupus erythematosus	*DRB1*0301*	2
	*DRB1*1501*	1.3
Ankylosing spondylitis	*B*27* (mainly *B*2705* and *B*2702*)	100-200
Celiac disease	*DQA1*0501-DQB1*0201* haplotype	7

[1]The odds ratio approximates values of increased risk of the disease associated with inheritance of particular HLA alleles. The data are from populations of European ancestry. Alleles of individual MHC genes (e.g., DRB1) are indicated by 4 numbers (e.g., 0301), based on serologic and molecular typing.
[2]Anti-CCP Ab, antibodies directed against cyclic citrullinated peptides. Data are from patients who test positive for these antibodies in the serum.
[3]SE refers to shared epitope, so called because it is a consensus sequence in the DRB1 protein (positions 70-74) present in multiple *DRB1* alleles.
(Courtesy of Dr. Michelle Fernando, Kings College, London.)

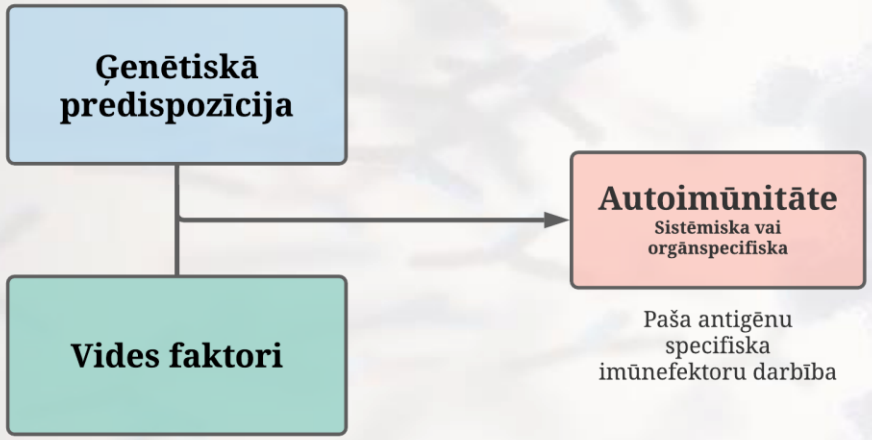
TABLE 15-3 Selected Non-HLA Genetic Polymorphisms Associated with Autoimmune Diseases

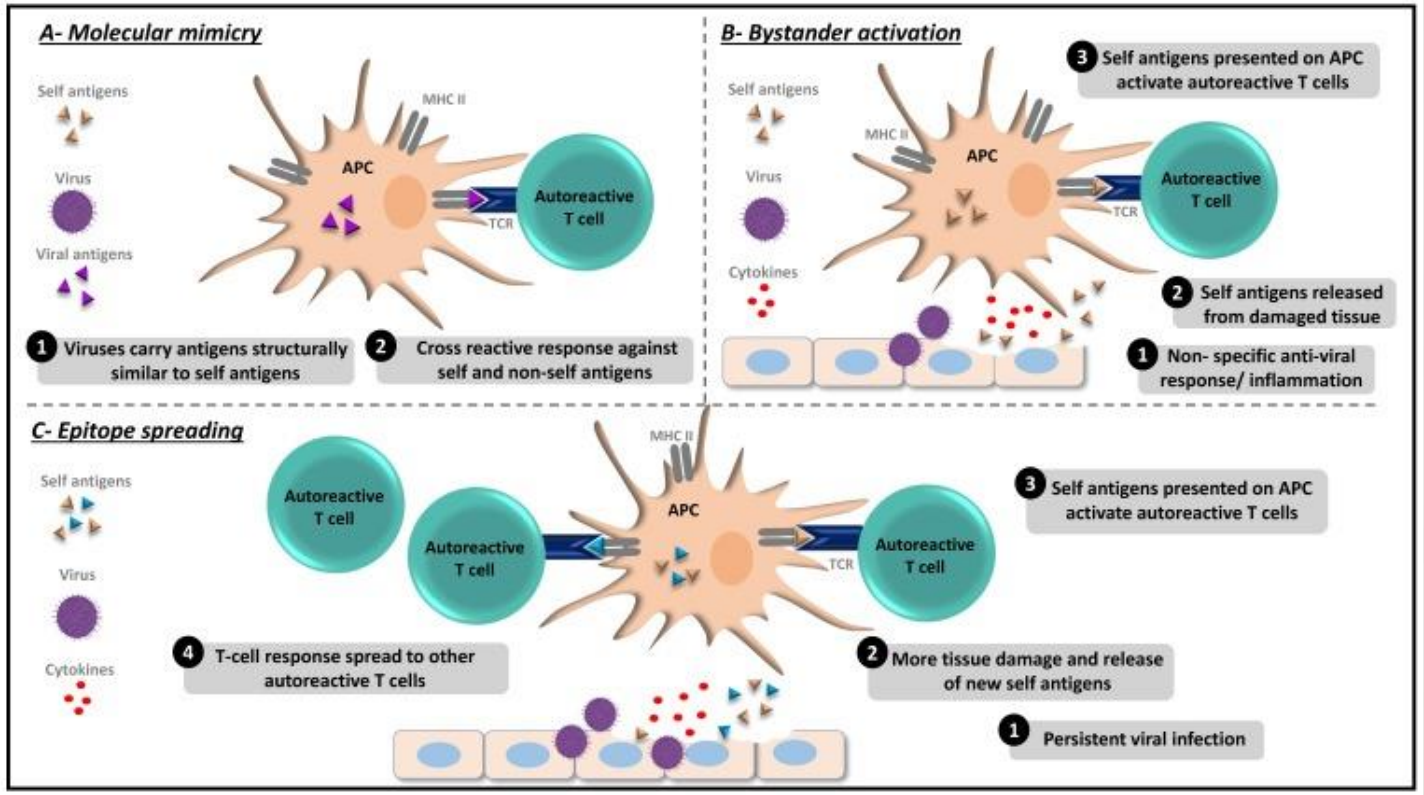
Gene of Interest	Function	Diseases
Genes Involved in Immune Regulation		
PTPN22	Protein tyrosine phosphatase; role in T and B cell receptor signaling	RA, T1D, IBD
CD2/CD58	Costimulation of T cells	RA, MS
IL23R	Component of IL-23 receptor; role in generation and maintenance of T_H17 cells	IBD, PS, AS
IL10	Downregulates expression of costimulators, MHC molecules, IL-12 in dendritic cells; inhibits T_H1 responses	IBD, SLE, T1D
CTLA4	Inhibitory receptor of T cells, effector molecule of regulatory T cells	T1D, RA
IL2/IL21	Growth and differentiation factors for T cells; IL-2 is involved in maintenance of functional Tregs	IBD, CeD, RA, T1D, MS
IL12B	p40 subunit of IL-12 (T_H1-inducing cytokine) and IL-23 (T_H17-inducing cytokine)	IBD, PS
BLK	B lymphocyte tyrosine kinase, involved in B cell activation	SLE, RA
IL2RA	IL-2 receptor α chain (CD25); role in T cell activation and maintenance of regulatory T cells	MS, T1D
Genes Involved in Responses to Microbes		
NOD2	Cytoplasmic sensor of bacteria	IBD
ATG16	Autophagy (destruction of microbes, maintenance of epithelial cell integrity)	IBD
IRF5, IFIH1	Type I interferon responses to viruses	SLE

AS, ankylosing spondylitis; *CeD*, celiac disease; *IBD*, inflammatory bowel disease; *MS*, multiple sclerosis; *PS*, psoriasis; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *T1D*, type 1 diabetes.
Data from Zenewicz L, Abraham C, Flavell RA, Cho J: Unraveling the genetics of autoimmunity, *Cell* 140:791-797, 2010, with permission of the publisher.

A. K. Abbas, A. H. Lichtman, and S. Pillai, *Cellular and molecular immunology*, Eighth edition. Philadelphia, PA: Elsevier Saunders, 2015.

Vīrusi un autoimunitāte





M. K. Smatti, F. S. Cyprian, G. K. Nasrallah, A. A. Al Thani, R. O. Almishal, and H. M. Yassine, "Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms," *Viruses*, vol. 11, no. 8, p. 762, Aug. 2019, doi: 10.3390/v11080762.

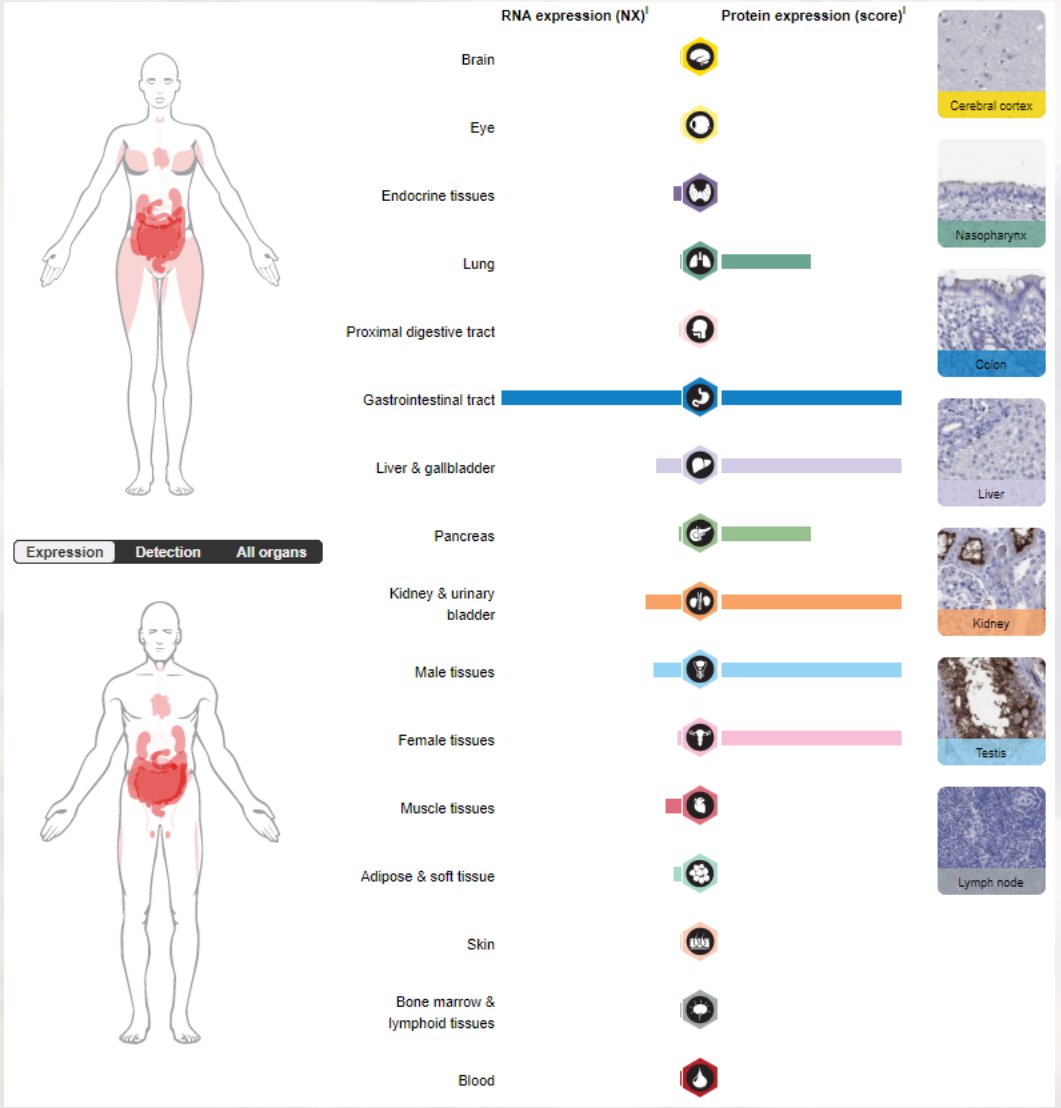
A – Vīrusa antigēnu epitopi līdzīgi paša organisma antigēniem. Vīrusa antigēnu prezentēšana aktivē imūno atbildi vērstu gan pret vīrusa, gan paša antigēniem
B – Audos esošās šūnas prezentē paša antigēnus un tur esošā imūnā atbilde pret vīrusu ierosina kostimulatoro molekulu ekspresiju kas ļauj aktivēties antigēnu specifiskām šūnām
C – Persistenta infekcija izraisa nemitīgu audu bojājumu, paša antigēnu atbrīvošanos un to prezentēšanu tālāk pastirpinot autoimūno procesu

Vīrusi un autoimunitāte

Autoimmune Disease	Virus	Organism	Proposed Mechanism	Study
Autoimmune myocarditis	Coxsackievirus B3	Mus musculus	Bystander activation	Rose, 2011 [106]
Autoimmune thyroiditis	Human herpesvirus 6A (HHV-6A)	Homo sapiens	-	Caselli et al., 2017 [107]
Cryoglobulinemia	Hepatitis C virus	Homo sapiens	-	Ogishi et al., 2016 [108]
Encephalitis (Human herpes encephalitis)	Herpes simplex virus	Homo sapiens	Molecular mimicry	Armangue et al., 2014 [109]
Encephalitis and chronic neurological sequelae	Herpes simplex virus	Homo sapiens	-	Kothur et al., 2017 [110]
Encephalitis, myasthenia gravis	Japenese encephalitis virus	Mus musculus	Molecular mimicry	He et al., 2018 [111]
Experimental autoimmune encephalomyelitis	Murine Gamma-Herpesvirus 68	Mus musculus	-	Casiraghi et al., 2015 [112]
Grave's disease	Esptein–Barr virus	Homo sapiens	-	Nagata et al., 2017 [113]
Guillain-Barré syndrome	Zika virus	Homo sapiens	Molecular mimicry	Lucchese and Kanduc, 2016 [114]
Hashimoto's disease	Esptein–Barr virus	Homo sapiens	-	Janegova et al., 2015 [115]
Immune thrombocytopenia, autoimmune hepatitis	Hepatitis C virus	Homo sapiens	-	Tampaki and Koskinas, 2014 [116]
Encephalomyelitis	Coronavirus	Mus musculus	-	Pewe and Perlman, 2002 [117]
Induced type 1 diabetes	Encephalomyocarditis-D virus	Mus musculus	Molecular mimicry	Choi et al., 2001 [118]
Islet autoimmunity	Enteroviruses	Homo sapiens	Molecular mimicry	Honkanen et al., 2017 [119]
Lung-restricted autoimmunity	Sendai virus	Mus musculus	-	Chiu et al., 2016 [120]
Multiple sclerosis	Esptein–Barr virus	Homo sapiens	Molecular mimicry	Guan et al., 2019 [121]
Multiple sclerosis	Theiler's virus	Homo sapiens	-	Miller et al., 2001 [122]
Multiple sclerosis	Varicella-zoster virus	Homo sapiens	-	Sotelo and Corona, 2011 [123]
Multiple sclerosis	Measles virus	Homo sapiens	-	Tucker and Andrew Paskauskas, 2008 [124]
Multiple sclerosis	Cytomegalovirus	Homo sapiens	Molecular mimicry	Vanheusden et al., 2017 [125]
Myasthenia gravis	West Nile virus	Homo sapiens/Mus musculus	Molecular mimicry	McBride et al., 2006 [126]
Myelopathy/tropical spastic paraparesis	Human T-lymphotropic virus type 1	Homo sapiens	-	Bangham et al., 2015 [127]
Polyarthritis	Hepatitis C virus	Homo sapiens	-	Zuckerman et al., 2000 [128]
Pulmonary Fibrosis	Gammaherpesvirus	Mus musculus	-	Bennion et al., 2019 [129]
Rheumatoid arthritis	Esptein–Barr virus	Homo sapiens	Epitope spreading	Dostál C et al., 1997 [130]
Rheumatoid arthritis	Cytomegalovirus	Homo sapiens	Epitope spreading	Pera et al., 2017 [131]
Pulmonary inflammation in lupus-prone mice	Influenza A virus	Mus musculus	Bystander activation & epitope spreading	Slight-Webb et al., 2015 [132]
Sjogren syndrome	Hepatitis C virus	Homo sapiens	Bystander activation	Ramos-Casals et al., 2005 [133]
Stromal keratitis	Herpes simplex virus	Homo sapiens	-	Deshpande et al., 2001 [134]
Stromal keratitis	Herpes simplex virus	Homo sapiens	-	Farooq and Shukla, 2012 [135]
Symmetric polyarthritis	Chikungunya virus	Homo sapiens	Epitope spreading	Goupil and Mores, 2016 [136]
Systemic lupus erythematosus	Cytomegalovirus	Homo sapiens	Epitope spreading	Chen et al., 2015 [137]
Systemic lupus erythematosus in porphyria cutanea tarda	Hepatitis C virus	Homo sapiens	Epitope spreading	Stölzel et al., 2002 [138]
Systemic lupus erythematous	Parvovirus B19	Homo sapiens	-	Ribeiro et al., 2015 [139]
Systemic lupus erythematous, lupus nephritis	Dengue virus	Homo sapiens	Epitope spreading	Steed and Stappenbeck, 2014 [140]
Systemic Vasculitis	Lassa Virus	Cynomolgus Macaques	-	Cashman et al., 2018 [141]
Thrombocytopenia	Hepatitis C virus	Homo sapiens	-	Dahal et al., 2017 [142]
Thyroiditis	Hepatitis C virus	Homo sapiens	Bystander activation	Ferri et al., 2017 [143]
TMEV-induced demyelinating disease	Theiler's murine encephalomyelitis virus	Mus musculus	Molecular mimicry	Olsberg et al., 1993 [144]
Type 1 diabetes mellitus	Coxsackievirus	Homo sapiens	Molecular mimicry	Eizirik and Op de Beeck, 2018 [145]
Type 1 diabetes mellitus	Coxsackievirus B1	Homo sapiens	Molecular mimicry	Laitinen et al., 2014 [146]
Type 1 diabetes mellitus	Cytomegalovirus	Homo sapiens		Pak et al., 1988 [77]
Type 1 diabetes mellitus	Rotavirus	Mus musculus	Bystander effect	Pane et al., 2014 [41]
Type 1 diabetes mellitus	Enteroviruses	Homo sapiens/Mus musculus	-	Stene and Rewers, 2012 [147]
Vasculitis	Hepatitis C virus	Homo sapiens	-	Cacoub et al., 2014 [148]

M. K. Smatti, F. S. Cyprian, G. K. Nasrallah, A. A. Al Thani, R. O. Almishal, and H. M. Yassine, "Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms," *Viruses*, vol. 11, no. 8, p. 762, Aug. 2019, doi: 10.3390/v11080762.

SARS-CoV-2 infekcija



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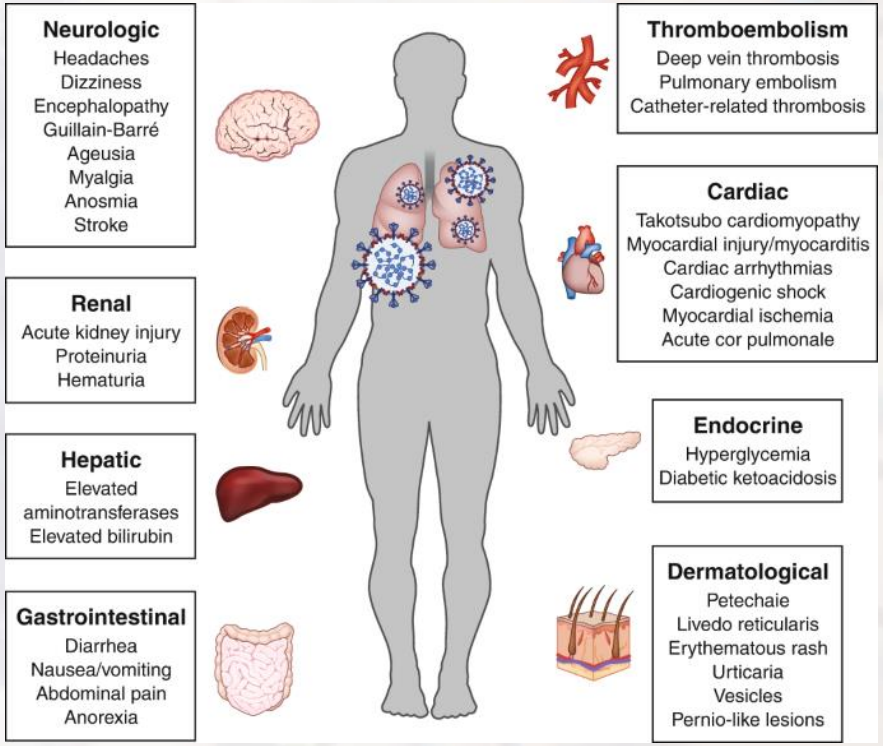
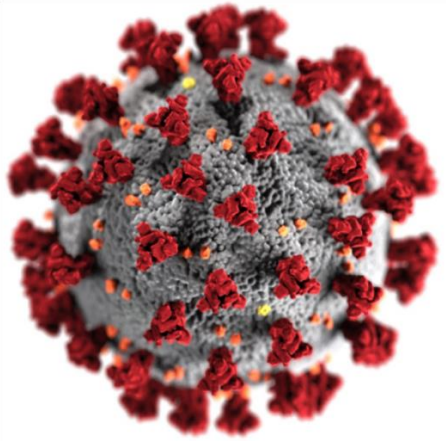
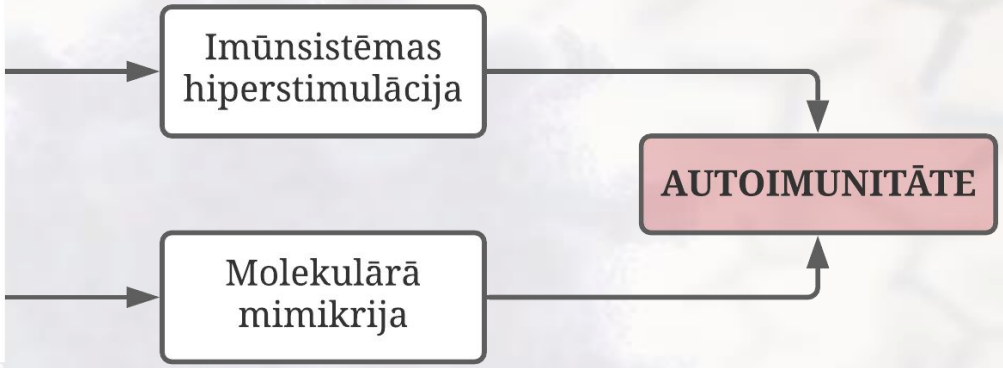


A. Gupta *et al.*, "Extrapulmonary manifestations of COVID-19," *Nature Medicine*, vol. 26, no. 7, Art. no. 7, Jul. 2020, doi: 10.1038/s41591-020-0968-3.c

SARS-CoV-2 un autoimunitāte



SARS CoV-2 infekcija



Editorial > Autoimmun Rev. 2021 Apr;20(4):102792. doi: 10.1016/j.autrev.2021.102792. Epub 2021 Feb 19.

The SARS-CoV-2 as an instrumental trigger of autoimmunity

Arad Dotan [1], Sylviane Muller [2], Darja Kanduc [3], Paula David [1], Gilad Halpert [4], Yehuda Shoenfeld [5]

Affiliations + expand

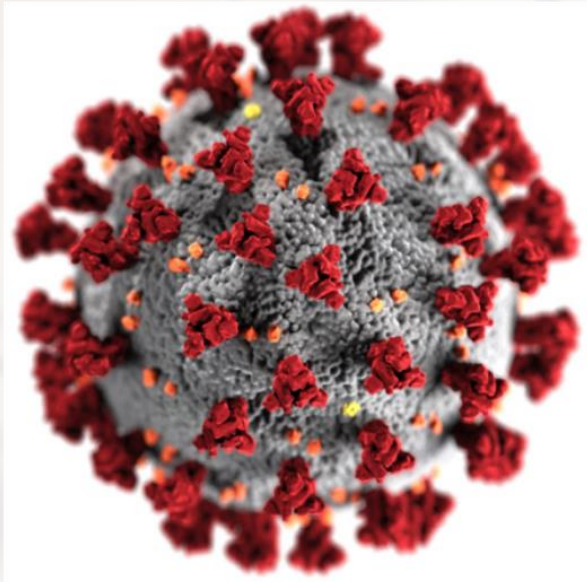
PMID: 33610751 PMCID: PMC7892316 DOI: 10.1016/j.autrev.2021.102792

frontiers in Immunology

Front Immunol. 2021; 12: 645013. PMCID: PMC7994612
Published online 2021 Mar 12. doi: 10.3389/fimmu.2021.645013 PMID: 33777042

Autoimmune and Rheumatic Manifestations Associated With COVID-19 in Adults: An Updated Systematic Review

Kuo-Tung Tang,[1,2,3] Bo-Chueh Hsu,[4] and Der-Yuan Chen[5,6,7,*]



SARS CoV-2 infekcija

Imūnsistēmas hiperstimulācija

Molekulārā mimikrija

AUTOIMUNITĀTE

SARS-CoV-2 un autoimunitāte – **HIPERSTIMULĀCIJA**

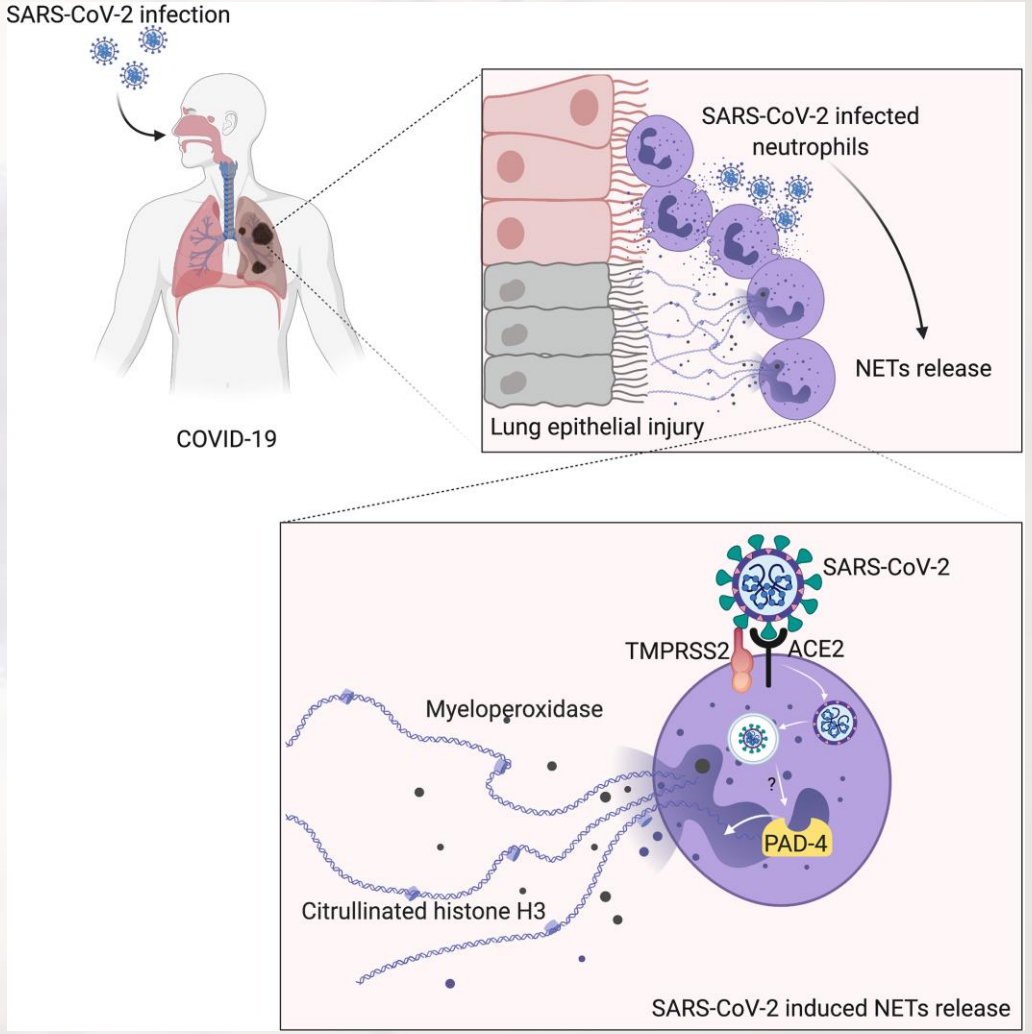
- Vairākkārt demonstrēts, ka COVID -19 pacientiem ir paaugstināti iekaisuma citokīnu līmeņi – **CITOKĪNU VĒTRA**
- COVID-19 pacientiem ir atrodamas izmaiņas cirkulējošo leikocītu veidos, piem., pazemināti **regulatoro T šūnu** līmeņi
- Pastirpināta **neitrofilu ekstracelulāro tīklu veidošanās** COVID-19 pacientiem

⇩

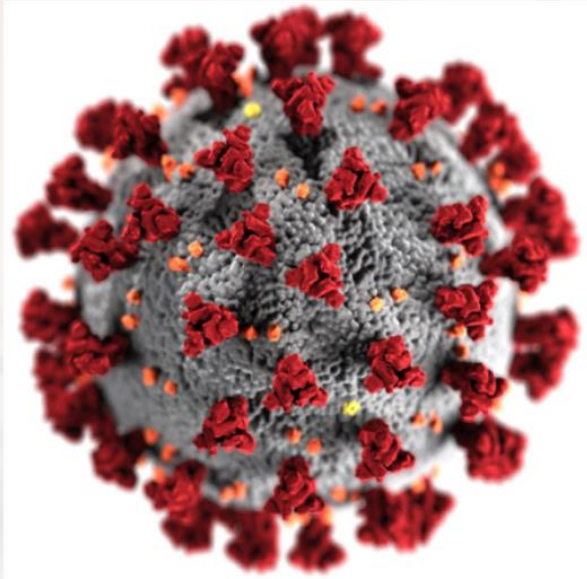
Ilgstošs, nekontrolēts iekaisums, audu bojājumi

⇩

AUTOIMUNITĀTE



F. P. Veras et al., "SARS-CoV-2–triggered neutrophil extracellular traps mediate COVID-19 pathology," Journal of Experimental Medicine, vol. 217, no. e20201129, Sep. 2020, doi: 10.1084/jem.20201129.



SARS CoV-2 infekcija

Imūnsistēmas hiperstimulācija

Molekulārā mimikrija

AUTOIMUNITĀTE

SARS-CoV-2 un autoimunitāte – **MOLEKULĀRĀ MIMIKRIJA**

- Analizē vīrusa un cilvēka aminoskābju sekvences, meklējot pārklājošos **peptīdus**

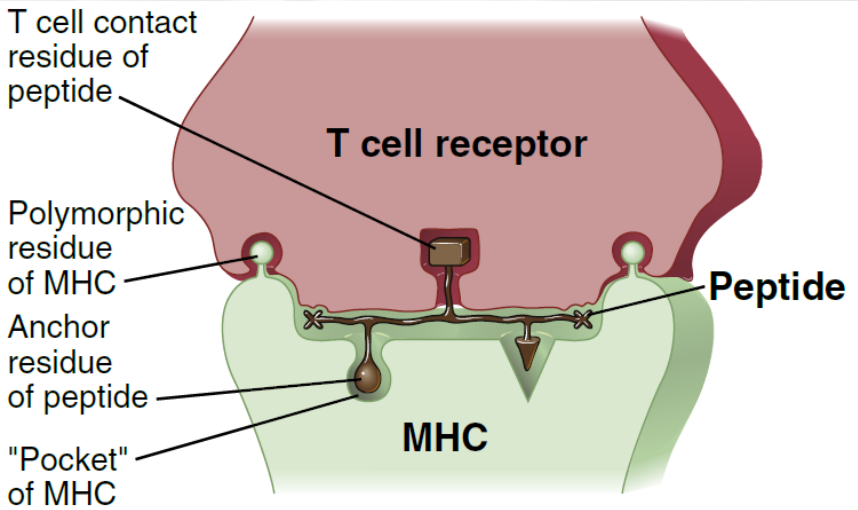
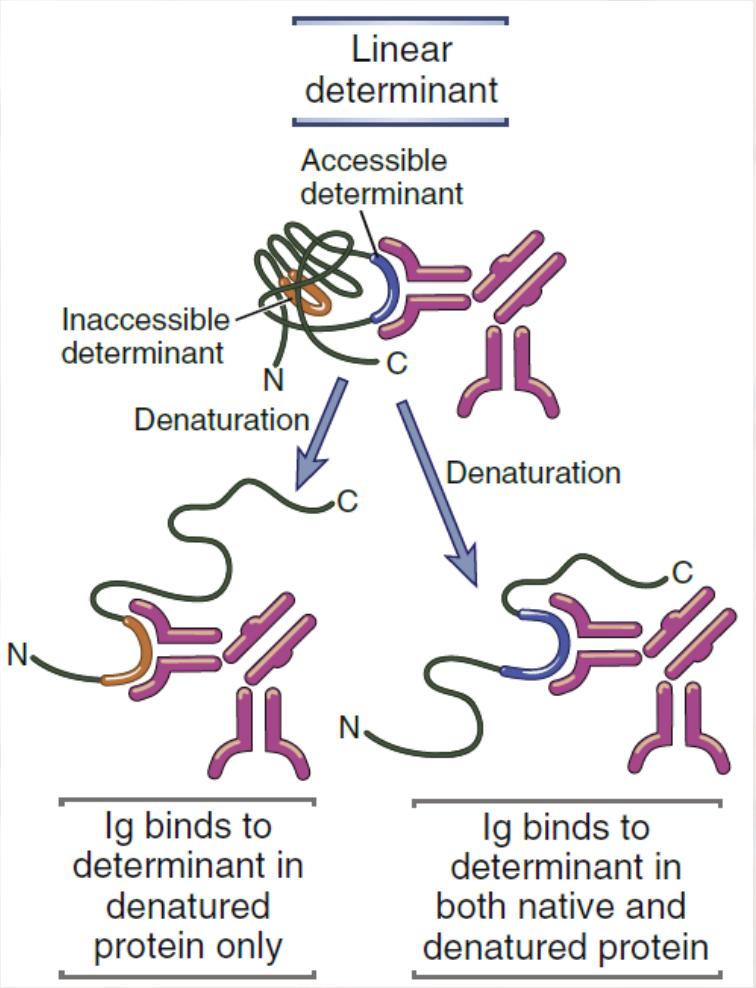


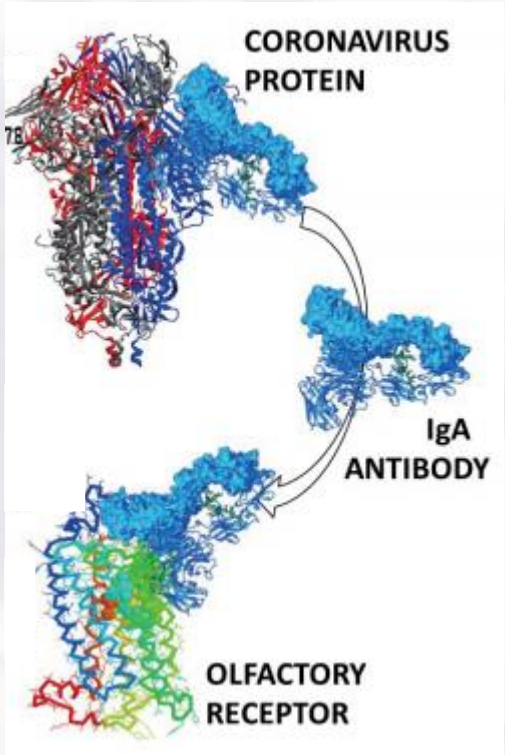
FIGURE 6-1 A model for T cell recognition of a peptide-MHC complex. This schematic illustration shows an MHC molecule binding and displaying a peptide and a T cell receptor recognizing two polymorphic residues of the MHC molecule and one residue of the peptide.



A. K. Abbas, A. H. Lichtman, and S. Pillai, *Cellular and molecular immunology*, Eighth edition. Philadelphia, PA: Elsevier Saunders, 2015.

SARS-CoV-2 un autoimunitāte – **MOLEKULĀRĀ MIMIKRIJA**

- Veicot vīrusa proteoma salīdzināšanu ar cilvēka, **atrasti vairāki peptīdi, kuri pārklājas**
- Līdzīgas aminoskābju sekvences starp cilvēku un vīrusu atrastas arī **ožas receptoru aminoskābju sekvencēs**



R. Root-Bernstein, "Anosmia-hyposmia and dysgeusia in COVID-19 may be due to SARS-CoV-2 protein mimicry of olfactory receptors," *RHINOL*, vol. 3, no. 3, pp. 148–151, Sep. 2020, doi: 10.4193/RHINOL/20.063.

Table 1
List and short description of 34 human proteins that share heptapeptides with SARS-CoV-2.

Shared 7-mer	Human proteins sharing heptapeptides with SARS-CoV-2*
SSRSSSR	Abl interactor 2
ALALLLL	Insulin-like growth factor-binding protein complex acid labile subunit
ALALLLL	Cerebellin-2
LLSAGIF	UPF0600 protein C5orf51
SSRSSSR	CLK4-associating serine/arginine rich protein
RGQGVPI	Putative uncharacterized protein encoded by the long intergenic non-protein coding RNA 346
ALALLLL	Cytochrome P450 2S1
ALALLLL	Delta and Notch-like epidermal growth factor-related receptor
GLTVLPP	FH1/FH2 domain-containing protein 3
LDKYFKN	Follistatin-related protein 1
RQLLFVV	Guanosine triphosphate-binding protein 10
IGAGICA	Hepatitis A virus cellular receptor 2
SSRSSSR	Hornerin
LFAAETL	Tyrosine-protein kinase ITK/TSK
LASFSAS	Maltase-glucoamylase, intestinal
LIRAAEI	Unconventional myosin-XVIIIa
QRMLLEK	Unconventional myosin-Vc
TGRLQSL	Neuron navigator 3
LIMLIIF	Sodium/potassium/calcium exchanger 2
IIFWFSL	Olfactory receptor 7D4
SLLSVLL	Orosomucoid 1-like protein 2
SSRSSSR	Oxysterol-binding protein-related protein 10
SSRSSSR	Pleckstrin homology domain-containing family G member 2
SRGGSQA	Ras-associating and dilute domain-containing protein
SSRSSSR	Solute carrier family 12 member 6
VLQLPQG	Prestin
AEGSRGG	snRNA-activating protein complex subunit 3
ALALLLL	Translocon-associated protein subunit delta
IVDTVSA	Alanine-tRNA ligase, mitochondrial
NASVVNI	Thyroid adenoma-associated protein
ALALLLL	Thrombospondin-3
LDDFVEI	Wolframin
SSRSSSR	Zinc finger CCCH domain-containing protein 18
SSRSSSR	Zinc finger Ran-binding domain-containing protein 2

A. Dotan, S. Muller, D. Kanduc, P. David, G. Halpert, and Y. Shoenfeld, "The SARS-CoV-2 as an instrumental trigger of autoimmunity," *Autoimmunity Reviews*, vol. 20, no. 4, p. 102792, Apr. 2021, doi: 10.1016/j.autrev.2021.102792.

SARS-CoV-2 un autoimunitāte – **AUTOANTIVIELAS**

COVID-19 pacientiem detektējamas vairākas autoantivielas

1. **Anti-fosfolipīdu antivielas**
2. **Neutralizējošas anti – 1 tipa interferonu antivielas**
3. **Anti-nukleārās antivielas**

... u.c.

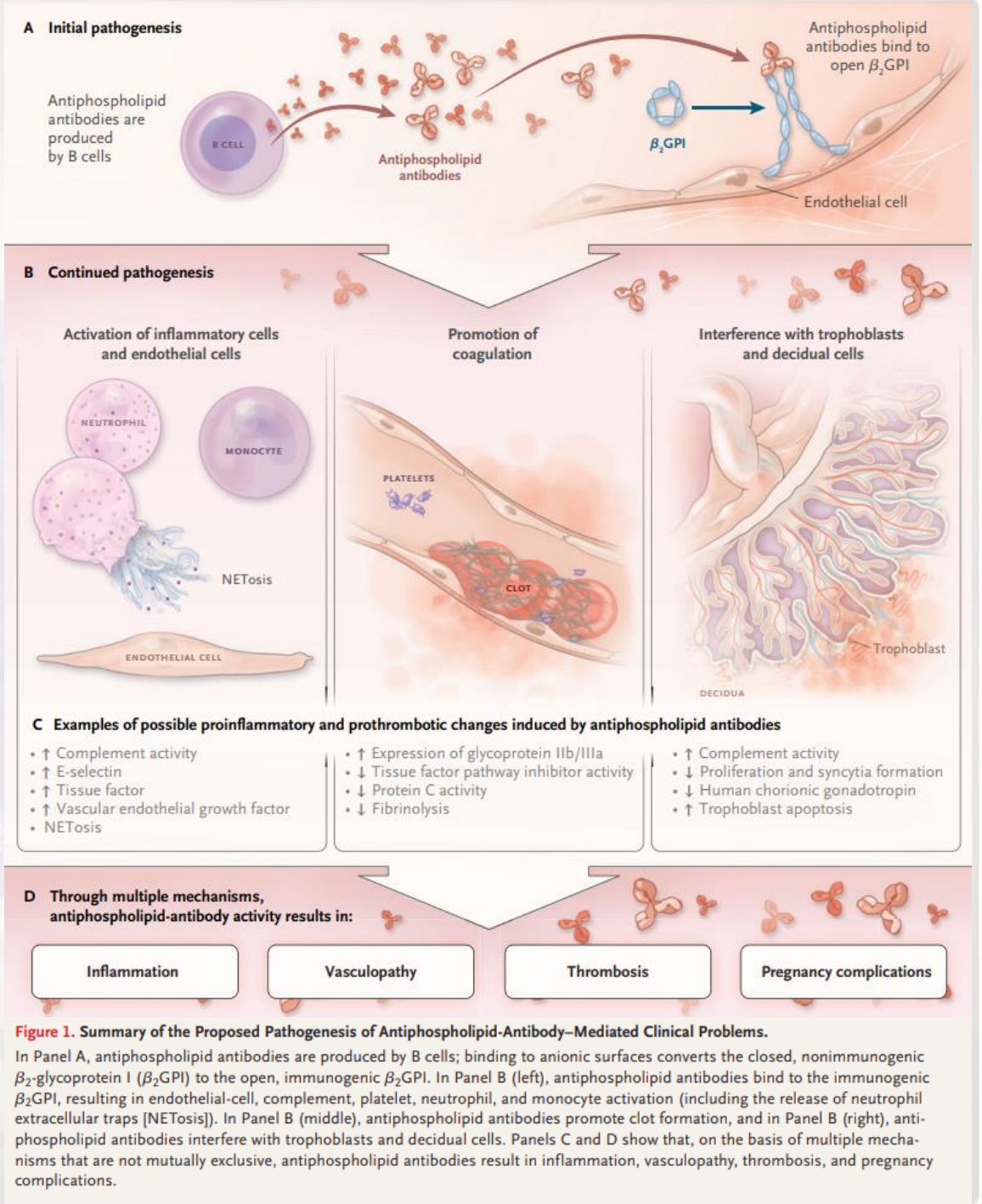


Figure 1. Summary of the Proposed Pathogenesis of Antiphospholipid-Antibody–Mediated Clinical Problems.

In Panel A, antiphospholipid antibodies are produced by B cells; binding to anionic surfaces converts the closed, nonimmunogenic β_2-glycoprotein I (β_2GPI) to the open, immunogenic β_2GPI. In Panel B (left), antiphospholipid antibodies bind to the immunogenic β_2GPI, resulting in endothelial-cell, complement, platelet, neutrophil, and monocyte activation (including the release of neutrophil extracellular traps [NETosis]). In Panel B (middle), antiphospholipid antibodies promote clot formation, and in Panel B (right), antiphospholipid antibodies interfere with trophoblasts and decidual cells. Panels C and D show that, on the basis of multiple mechanisms that are not mutually exclusive, antiphospholipid antibodies result in inflammation, vasculopathy, thrombosis, and pregnancy complications.

D. Garcia and D. Erkan, "Diagnosis and Management of the Antiphospholipid Syndrome," *New England Journal of Medicine*, vol. 378, no. 21, pp. 2010–2021, May 2018, doi: 10.1056/NEJMra1705454.

SARS-CoV-2 un autoimunitāte – **AUTOIMŪNĀS SLIMĪBAS**

- **Gijēna-Barē sindroms**
- Autoimūnās vairogdziedzera slimības
- **Autoimūna hemolītiskā anēmija**

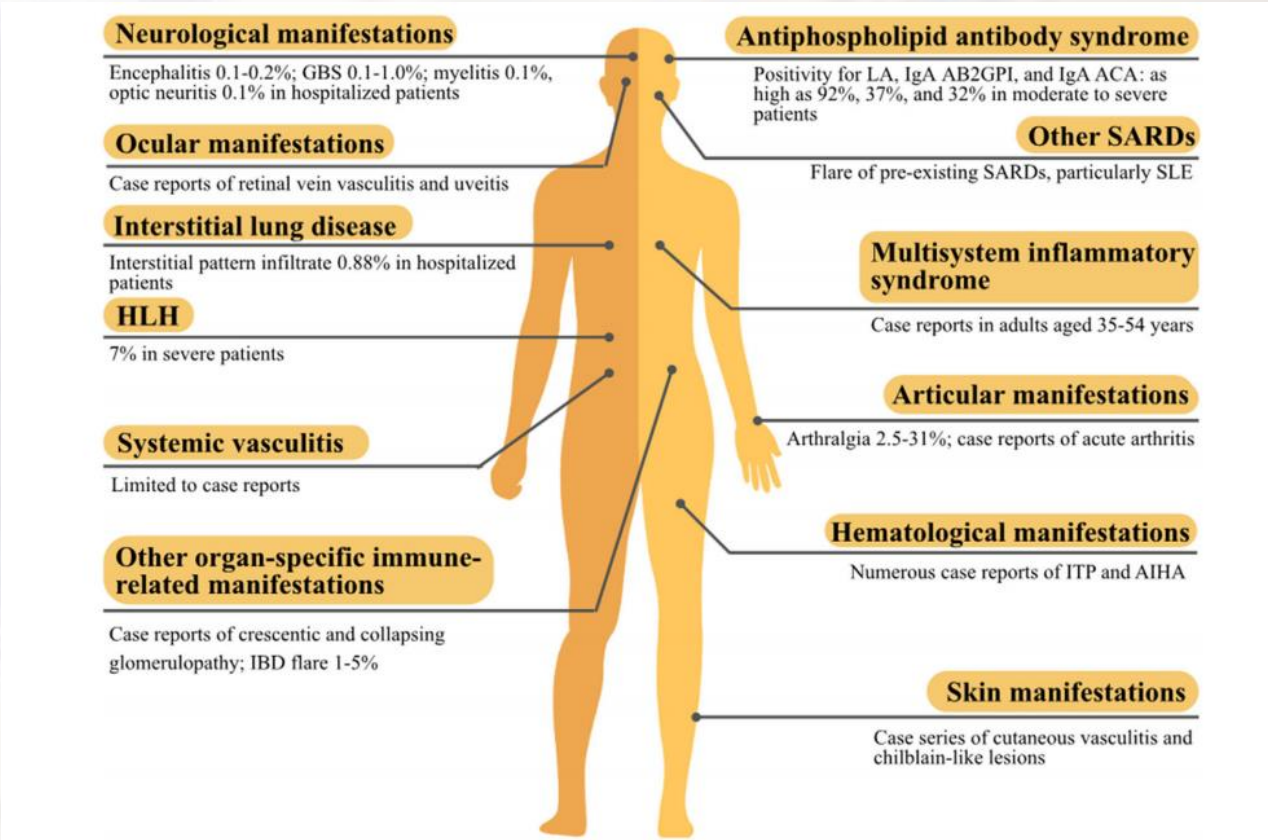
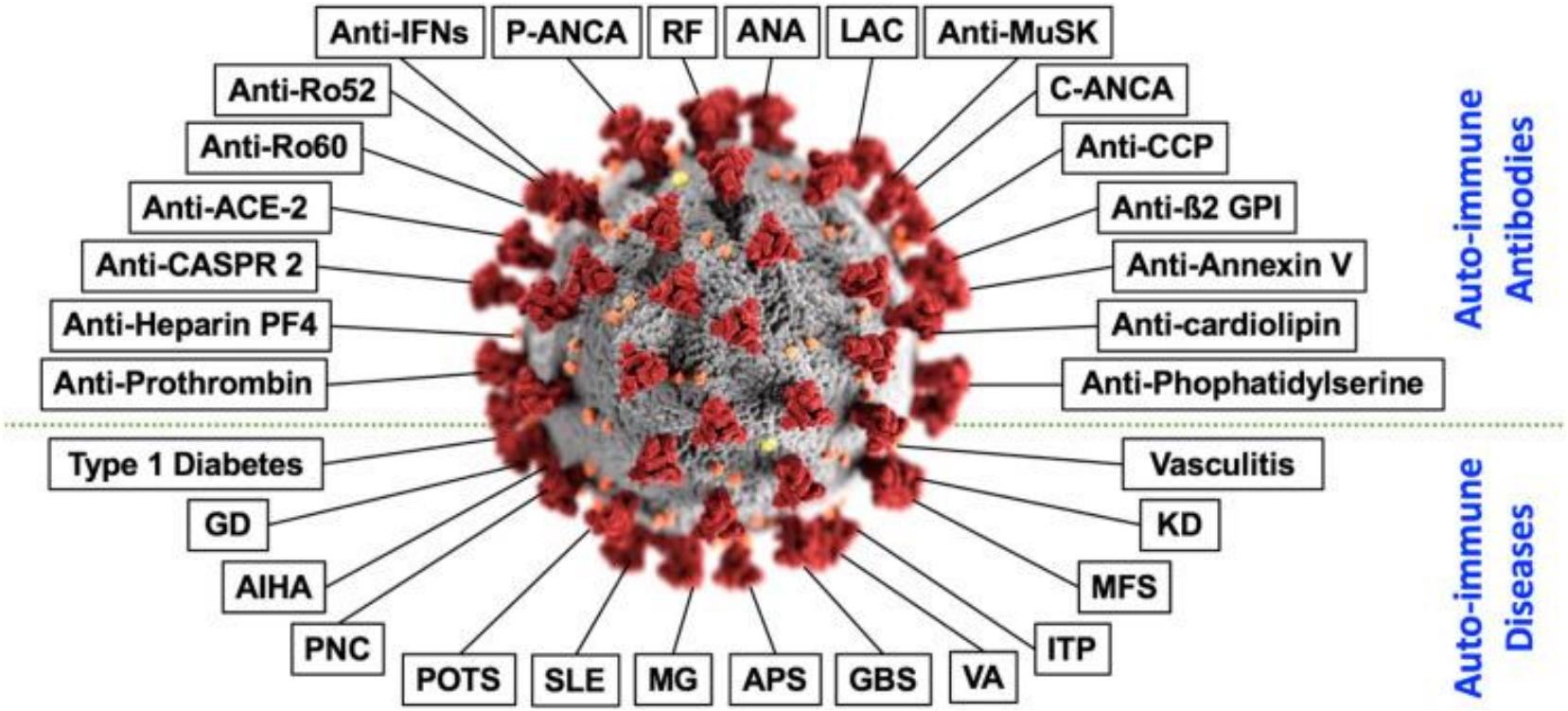


FIGURE 3 | The summary of autoimmune and rheumatic manifestations associated with the coronavirus disease 2019 (COVID-19). AB2GPI, anti-β2glycoprotein I antibody; ACA, anticardiolipin antibody; AIHA, autoimmune hemolytic anemia; GBS, Guillain-Barré syndrome; HLH, hemophagocytic lymphohistiocytosis; IBD, inflammatory bowel disease; ITP, immune thrombocytopenic purpura; LA, lupus anticoagulant; SARD, systemic autoimmune rheumatic disease; SLE, systemic lupus erythematosus.

K.-T. Tang, B.-C. Hsu, and D.-Y. Chen, "Autoimmune and Rheumatic Manifestations Associated With COVID-19 in Adults: An Updated Systematic Review," *Front Immunol*, vol. 12, Mar. 2021, doi: 10.3389/fimmu.2021.645013.



PALDIES!

A. Dotan, S. Muller, D. Kanduc, P. David, G. Halpert, and Y. Shoenfeld, "The SARS-CoV-2 as an instrumental trigger of autoimmunity," *Autoimmunity Reviews*, vol. 20, no. 4, p. 102792, Apr. 2021, doi: 10.1016/j.autrev.2021.102792.

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