

## Molecular mimicry and autoimmunity in the time of COVID-19

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### ABSTRACT

Infectious diseases are commonly implicated as potential initiators of autoimmune diseases (ADs) and represent the most commonly known factor in the development of autoimmunity in susceptible individuals. Epidemiological data and animal studies on multiple ADs suggest that molecular mimicry is one of the likely mechanisms for the loss of peripheral tolerance and the development of clinical disease. Besides molecular mimicry, other mechanisms such as defects in central tolerance, nonspecific bystander activation, epitope-determinant spreading, and/or constant antigenic stimuli, may also contribute for breach of tolerance and to the development of ADs. Linear peptide homology is not the only mechanism by which molecular mimicry is established. Peptide modeling (i.e., 3D structure), molecular docking analyses, and affinity estimation for HLAs are emerging as critical strategies when studying the links of molecular mimicry in the development of autoimmunity. In the current pandemic, several reports have confirmed an influence of SARS-CoV-2 on subsequent autoimmunity. Bioinformatic and experimental evidence support the potential role of molecular mimicry. Peptide dimensional analysis requires more research and will be increasingly important for designing and distributing vaccines and better understanding the role of environmental factors related to autoimmunity.

### 1. Introduction

Autoimmune diseases (ADs) are a chronic and clinically heterogeneous group of diseases that affect approximately one in ten individuals [1], with a steadily increasing incidence throughout westernized societies [2]. Although clinically diverse, autoimmune disorders share common immunopathogenic mechanisms and risk factors, a phenomenon coined as autoimmune tautology (i.e., ADs are similar to each other) [3]. Molecular mimicry, defined as similarities between foreign and self-peptides that favor activation of autoreactive T or B cells in susceptible individuals [4], is often considered a primary mechanism for autoimmunity development following environmental exposure.

The first description in the late 60s of molecular mimicry was by Zabriskie and Freimer [5], and it has been widely discussed as a mechanism for the loss of peripheral tolerance [4,6–9]. Natural infection is commonly considered the leading pathway for this phenomenon. Other environmental factors, such as chemicals, drugs, and vaccines, also have the potential to lead to autoimmunity not only *via* molecular

mimicry but also by bystander activation, epitope-determinant spreading, and/or hapten carrier [10–12].

Despite substantial research on the homology of several microbial peptides/proteins and human tissue peptides/proteins, the intricacies of how microbial proteins are involved in the etiology of ADs remain unknown. Host factors (e.g., defects in central or peripheral tolerance, human leukocyte antigens [HLA], and *non-HLA* polymorphisms) [13–20], T-cell receptors (TCRs) with diverse heterodimers or homodimers of  $\alpha$  and  $\beta$  chains configuration [21], microbiome [22], and immunosenescence [23], also play a critical role in ADs susceptibility when molecular mimicry is present in genetically susceptible individuals.

Four types of molecular mimicry have been previously proposed [24–29]; 1) Type 1: “complete identity at the protein level between a microorganism and its host” (e.g., A human protein hijacked by the virus, and later presented as antigen by antigen presenting cells); 2) Type 2: “homology at the protein level between a microorganism and its host, of a protein encoded by the microorganism”; 3) Type 3: “common or similar native or glycosylated amino acid sequences or epitopes shared between the

Abbreviations: APC, Antigen presenting cell.

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**List of abbreviations**

ABCs	Age-associated B cells	KD	Kawasaki disease
ACE2	Angiotensin-converting enzyme 2	MBP	Myelin basic protein
ADs	Autoimmune diseases	ME/CFS	Myalgic encephalomyelitis/chronic fatigue syndrome
ANAs	Antinuclear antibodies	MERS-CoV	Middle East respiratory syndrome coronavirus
BAFF	B cell-activating factor	MHC	Major histocompatibility complex
BCR	B cell receptor	MIP-1 $\alpha$	Macrophage inflammatory protein-1 $\alpha$
C	Constant	MIS-C	Multisystem inflammatory syndrome in children
CMV	Cytomegalovirus	MS	Multiple sclerosis
COMPASS-31	Composite Autonomic Symptom Score 31	NETs	Neutrophil extracellular traps
COVID-19	Coronavirus disease 2019	NF- $\kappa$ B	Nuclear factor- $\kappa$ B
DN2	Double negative	NS	Non-structural protein
Dsg	Desmoglein	PCS	Post-COVID syndrome
EAE	Experimental autoimmune encephalomyelitis	PF	Pemphigus foliaceus
EAU	Experimental autoimmune uveitis	PolyA	Polyautoimmunity
EBV	Epstein-Barr virus	PR3	Proteinase 3
EFB	Extrafollicular B cells	PRR	Pattern recognition receptor
ES	Epitope spreading	RA	Rheumatoid arthritis
FS	Fogo Selvagem	RBD	Receptor binding protein
GBS	Guillain-Barré syndrome	RF	Rheumatoid factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor	S	Protein spike
HBV	Hepatitis B virus	SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
HCRTR2	Hypocretin Receptor 2	SLE	Systemic lupus erythematosus
HDM	House dust mites	SS	Sjögren's syndrome
HLA	Human leukocyte antigen	SSc	Systemic sclerosis
HPV	Human papillomavirus	ssRNA	Single-stranded RNA
HSV-1	Herpes simplex virus-1	T1D	Type 1 diabetes
IFN	Interferon	TCR	T cell receptor
IL	Interleukin	Tg	Thyroglobulin
ITP	Immune thrombocytopenia	TMEV	Theiler's murine encephalomyelitis virus
J	Joining	TPO	Thyroid peroxidase
		V	Variable
		$\beta$ 2GP1	$\beta$ 2-Glycoprotein 1

microorganisms or environmental agents and its host"; and 4) Type 4: "structural similarities between the microbe or environmental agents and its host". In theory, any type could induce diverse immune responses; however, type 3 is the most commonly linked to autoimmunity (similar but not exactly the same protein sequence). Recent analyses suggest that structural homology (Type 4), besides linear peptide homology, is a differential factor for the emergence of autoreactivity, especially in situations of hidden or cryptic epitopes defined in secondary, tertiary, or quaternary protein structure [30].

There are four well-defined criteria for considering molecular mimicry as a mechanism for autoimmunity [25,31]: 1) "evidence of similarity between a host epitope and an epitope of a microorganism or environmental agent"; 2) "detection of antibodies or T-cells that cross-react with both epitopes in patients with ADs"; 3) "epidemiological link between exposure to the environmental agent or microbe and development of ADs"; and 4) "the reproducibility of autoimmunity in an animal model following sensitization with the appropriate epitopes either following infection with the microbe or exposure to the environmental agent." However, most pathogens associated with autoimmunity do not fulfill these criteria and could be considered an epiphenomenon (as previously described) [4]. Thus, it raises the question of whether the current approaches to studying autoimmunity associated with molecular mimicry are enough to uncover the intricate pathways related to this complex phenomenon, as several diseases with different peptide homologies have been reported (Table 1) [29,32–84]. In addition, these hypotheses are difficult to prove in an outbred population like humans, particularly for rare events/diseases.

The coronavirus disease 2019 (COVID-19) pandemic has emphasized the potential role of viral infections in developing autoimmunity. New-onset autoantibodies are commonly found in acute COVID-19 [85],

latent polyautoimmunity (PolyA) influences the outcomes in hospitalized patients [86], and anti-interferon (IFN) antibodies have been implicated in mortality in male patients [87]. Interestingly, this phenomenon of latent autoimmunity persists in patients with post-COVID syndrome (PCS), and in about 12% of patients the incidence of latent autoimmunity increases over time [88]. Intriguingly, many reports have shown the appearance of overt ADs during PCS, including organ-specific and systemic conditions [88,89], indicating that autoimmunity after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is common [90].

In rare cases, several autoimmune and inflammatory diseases have been reported following vaccination against SARS-CoV-2 [90]. There have also been reports of flare-ups of ADs after vaccination [90]. These data indicate that susceptible individuals with or without prior evidence of autoimmunity can develop overt ADs associated with natural infections or vaccination. Herein, we present an updated review of the new evidence on molecular mimicry and autoimmunity, the new approaches to studying this mechanism, and its likely role in ADs following vaccination.

## 2. Antigenic mimicry, mimotopes, and autoreactivity

Peptide binding by major histocompatibility complex (MHC) molecules presented to T cells is based on the sequence of 8–10 amino acids presented by MHC class I, and 14–18 amino acids presented by MHC class II to CD8<sup>+</sup> and CD4<sup>+</sup> T cells, respectively. TCRs have specificity for the specific MHC-bound peptide, a phenomenon known as MHC restriction [91–93]. The process of TCR production requires recombination of the variable (V), joining (J), and the constant (C) regions that produce the diversity of T-cell responses [94]. VJ genes coding the

**Table 1**  
Infections, autoimmune diseases, and molecular mimicry.

Infectious agent	Autoimmune disease	Structural homology	References
Viruses			
Adenovirus	AIH	Mimicry between viral proteins and the CYP2D6.	[32]
CMV	AIH	Molecular similarities between the CYP2D6 and viral proteins.	[33]
	AITD	Homology between viral and TPO structure.	[34]
PBC	GBS	MOESIN, a cytoskeletal protein, and the gangliosides GM2, GalNAc-GD1a, and GD2 exhibit molecular similarity with CMV structures.	[29]
		Mimicry between the human PDC-E2 and the microbial PDC-E2 and induction of PDC-E2-specific AMAs.	[35]
	SLE	Molecular mimicry between the virus's pp65 and TAF9 and between the virus's non-structural intranuclear protein UL44 and the SLE nuclear antigens dsDNA, ku70, and nucleolin.	[36]
SSc		Mimicry between the CMV UL94 protein and human immunodominant peptide (i.e., GGIGGAGIWLVV). Topoisomerase I amino acids 121–126 share homology with the CMV late protein UL70.	[37,38]
	T1DM	Mimicry of the human CMV major DNA-binding protein with the glutamic acid decarboxylase 65.	[39]
EBV	AITD	To produce TRAbs and send co-stimulatory signals to autoreactive T cells, EBV-produced LMP-1 enables EBV-infected autoreactive B cells.	[40,41]
	MS	The similarity between the MBP and the EBNA1. Homology between the DRB1*15:01-restricted MBP and the DRB5*01:01-restricted EBV peptide.	[42,43, 84]
PBC		Specifically, PDC-E2 mimicry between humans and microbes and the induction of PDC-E2-specific AMAs.	[35]
	SS	Homology between viral EBER1 and EBER2 proteins and La antigen, as well as between viral EBVNA2 protein and Ro60 antigen.	[44]
SLE		Cross-reaction between PPPGRRP of EBVNA-1 that cross-reacted with PPPGMRPP of Sm, amino acids 35–58 of EBVNA-1 that cross-reacted with amino acids 95–119 of Sm, and amino acids 58–72 of EBVNA-1 that cross-reacted with amino acids 169–180 of Ro.	[45–48]

**Table 1 (continued)**

Infectious agent	Autoimmune disease	Structural homology	References
Enteroviruses	T1DM	Homology between the viral protein 1 (PALTAVETGA/HT) of enterovirus and the β-cell antigen tyrosine phosphatase IA-2.	[49]
	HBV	AU	Molecular mimicry between HBV structures and self-antigens (retina 5-Ag).
GBS		Cross-reaction between HBV polymerase and MBP.	[29]
MS		Cross-reaction between HBV-DNA polymerase and MBP.	[50]
HCV	SS	Sequence similarities to SSB/La decapeptides with HBV.	[51]
	AIH	Mimicry between the CYP2D6 and viral proteins.	[52]
HBRV	AITD	Homologous epitopes of the HCV with anti-LKM-1 Ab, TPO, Tg, NIS, TSHR and pendrin.	[34,53]
	CV	Molecular mimicry between HCV antigens and liver-derived human autoantigens (PAFAH1B3).	[54]
HEV	PBC	Homologous epitopes of the microbial PDC-E2 and the human PDC-E2 and therefore, induction of PDC-E2-specific AMAs.	[35]
	GBS	Cross-react between HEV structures and GM1 and GM2.	[29]
HIV	SLE	The polyclonal proliferation of B cells is associated with hyper-gamma globulinemia and the development of neutralizing antibodies against Env epitopes (CH98) that cross-react with ds-DNA.	[36]
HHV-6	MS	Homology between U24 peptide of the virus and MBP.	[55]
HPV	SLE	Cross-reaction between complement proteins, viral proteins, NK receptors, La autoantigen, methyl-CpGbinding protein 2, proteins P0 and P1, Sm protein B/B0, and Sm protein D.	[56]
HSV-1	GBS	Sequence similarities between HSV-1 structures and GQ1b ganglioside, altered ganglioside-related gene expression.	[29]
	AIH	Mimicry between the CYP2D6 and viral proteins.	[57]
HSV-2	MG	The HuAChR α-subunit 160–167 peptide in MG patients shared a homologous domain with herpes simplex virus glycoprotein D residues 286–293.	[58]
	GBS	Enhancing ganglioside-related gene expression (β3-galactosyltransferase-IV, α2,8-sialyltransferase-I).	[29]

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Table 1 (continued)

Infectious agent	Autoimmune disease	Structural homology	References
HTLV-1	SLE	Homology between HRES-1/p28 protein and HTLV-1 gag p24 protein. Molecular mimicry between antiviral HRES-1/p28 antibodies and 70 K U1snRNP SLE autoantigen.	[36]
PVB19	AIH	The similarity between VP2 of the virus and ssDNA.	[59]
	APS	Cross-reactivity between VP2 of the virus and cardiolipin.	[59]
	ITP	Cross-reactivity between NS1 of the virus and platelet membrane GPIIb/IIIa.	[59]
	MS	Structural similarities between the virus and MBP.	[59]
	Myositis	Molecular mimicry between viral VP2 and ssDNA.	[59]
	RA	Molecular mimicry between viral VP2 and collagen II and ssDNA.	[59]
	SLE	Homology between viral VP2 and ssDNA, keratin and cardiolipin. VP-1 might play a role in viral entry into the cell and expanding phospholipids epitopes that will ultimately lead to aPL antibodies.	[59,60]
Rotavirus	AU	Shares amino acid homologies between viral VP4 protein and retinal S-antigen peptide.	[61]
	Coeliac disease	Molecular mimicry between viral VP7 and human Transglutaminase.	[61]
	Pemphigus vulgaris	Sequence homology between viral VP6 and human Desmoglein-3.	[61]
	T1DM	Potentially cross-reactivity between viral VP7 and pancreatic islet autoantigens (IA-2 and GAD65).	[61]
TTV	SLE	Molecular mimicry between TTV peptide ORF2a and HRES-1/p28, which acts as a nuclear autoantigen and with EBV antigens (EBV-LF3 and EBVNA-3C).	[36]
ZIKV	GBS	Sequence homology between ZIKV structures GA1, GM2, GD1a, and GB1b gangliosides.	[62]
<b>Bacteria</b> <i>B. burgdorferi</i>	AITD	The similarity between residues 112–205, 127–150, 141–260, 299–383, and 620–697 of TSHR, and the flagellar motor rotation protein A, outer surface protein A, and DNA recombinase/ATP dependent helicase of <i>B. burgdorferi</i> .	[34]
<i>C. jejuni</i>	GBS	Carbohydrate mimicry (Galβ1–3GalNAcβ1–4 (NeuAcα2–3)Galβ1–)	[63,64]

Table 1 (continued)

Infectious agent	Autoimmune disease	Structural homology	References
<i>E. coli</i>	PBC	between the bacterial lipooligosaccharide and human GM1 ganglioside.	[65,66]
	RA	Mimicry between the human PDC-E2 and the <i>E. coli</i> PDC-E2. Heat shock protein (i.e., DnaJ) contains a QKRRAA motif present in the HLA-DRB1 shared epitope.	[67]
<i>P. gingivalis</i>	RA	The <i>P. gingivalis</i> enolase and the human α-enolase at the 17-amino acid immunodominant regions are similar. <i>P. gingivalis</i> may activate the citrullination of proteins through the bacterial peptidylarginine deiminase.	[68]
<i>P. mirabilis</i>	RA	Cross-reactivity between the hemolysin, urease C, urease F enzymes, and the human proteome.	[69]
<i>Y. enterocolitica</i>	AITD	Mimicry between the TSH-R (residues 22–272, 186–330, 319–363, and 684–749) and the envelope proteins of <i>Y. enterocolitica</i> (YopM, Ysp, exopolysaccharuronase, and SpyA).	[34,70,71]
<i>Y. pseudotuberculosis</i>	AITD	Cross-reactivity between <i>Y. pseudotuberculosis</i> and TSH-R.	[72]
<b>Parasites</b> <i>Leishmania</i> sp.	SLE	Molecular mimicry between Glucose-6-phosphate isomerase, Histone deacetylase 3, Triosephosphate isomerase, Small nuclear ribonucleoprotein G and Small ribonucleoprotein associated proteins B and autoantigen present in SLE.	[73]
<i>Trypanosoma</i> sp.	SLE	The similarity between more than thirty-six parasite antigens and autoantigens involved in SLE.	[74]
<b>Vaccines</b>	Influenza vaccine	Homology between the surface-exposed influenza nucleoprotein A and the extracellular domain of hypocretin 2 receptor in narcolepsy. Suspected homology between influenza proteins and peripheral nerve structures in GBS (unknown exactly homology).	[75,76]
	HPV vaccine	Peptide homology between HPV with lupus Ku autoantigen proteins (i.e., p86, p70), lupus brain antigen 1 homolog, natural killer cell IgG-like receptors, complement and complement receptor	[77,78]

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Table 1 (continued)

Infectious agent	Autoimmune disease	Structural homology	References
		CD19 in SLE. Thirty-four pentamers from the viral capsid protein are shared with human proteins that are associated with cardiovascular diseases (i. e., the PSEA sequence of the HPV16 shares homology with the human Q99959 protein). Likely associated with POTS.	
	HBV vaccine	The HBV polymerase could act as an autoantigen and induce autoimmune demyelination in multiple sclerosis. HBV vaccination can induce anti-β2GPI antibodies as a result of β2GPI binding to recombinant hepatitis B surface antigen (rHBsAg). Furthermore, rHBsAg targets the fifth domain on the phospholipid binding site of β2GPI.	[79–81]
<b>Others</b>			
Sand fly	Brazilian pemphigus foliaceus	Cross-reactivity between LMJ11 (a sand fly saliva protein) and desmoglein 1 and anti-desmoglein 1 monoclonal antibodies.	[82]
House dust mites	Vasculitis	Cross-reactivity between proteinase 3 (PR3) expressed on the neutrophil surface that will ultimately lead to tissue damage in small vessels	[83]

AIH: autoimmune hepatitis; AITD: autoimmune thyroid disease; AMA: anti-mitochondrial antibodies; APS: antiphospholipid syndrome; aPL: anti-phospholipid; AU: autoimmune uveitis; *B. burgdorferi*: *Borrelia burgdorferi*; CMV: cytomegalovirus; CV: cryoglobulinemia vasculitis; *C. jejuni*: *Campylobacter jejuni*; EBEB: EBV-encoded small RNA; EBV: Epstein-Barr virus; EBVNA: EBV nuclear antigen; EBNA1: EBV nuclear antigen 1; *E. coli*: *Escherichia coli*; GAD65: glutamic acid decarboxylase 65; GBS: Guillain-Barré syndrome; Gp: glycoprotein; HAM/TSP: HTLV-1 associated myelopathy/tropical spastic paraparesis; HBRV: human Betaretrovirus; HBV: hepatitis B virus; HCV: hepatitis C virus; HERV: human endogenous retroviruses; HEV: hepatitis E virus; HHV-6A: human herpesvirus 6A; HPV: human papilloma virus; HRES-1: HTLV-1-related endogenous sequence; HSP: heat shock proteins; HSV: herpes simplex virus; HTLV: human T-cell lymphotropic virus; HIV: human immunodeficiency virus; IL, interleukin; ITP, immune thrombocytopenia; LKM-1 Ab: liver/kidney Microsomal Antibody type 1; LMP: latent membrane protein; MBP: myelin basic protein; MG: myasthenia gravis; MOESIN: membrane-organising extension spike protein; NAG: neuroblastoma-amplified gene; NIS: Sodium Iodide Symporter; NS: non-structural protein; ORF: open reading frame; PBC: primary biliary cholangitis; PDC: pyruvate dehydrogenase; pp65: phosphoprotein 65; *P. gingivalis*: *Porphyromonas gingivalis*; *P. mirabilis*: *Proteus mirabilis*; POTS: Postural orthostatic tachycardia syndrome; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; SS: sjogren's syndrome; SSC: systemic sclerosis; T1DM: type 1 diabetes mellitus; Tg: thyroglobulin; TAF9: TATA-box binding protein associated factor 9; TPO: thyroid peroxidase; TSHR: thyroid stimulating hormone receptor; TTV: torque teno virus; VZV: varicella zoster virus; *Y. enterocolitica*: *Yersinia enterocolitica*; *Y. pseudotuberculosis*: *Yersinia pseudotuberculosis*; ZIKV: zika virus. COVID-19 vaccines may also induce autoimmunity (see text).

TCRs can produce up to  $10^{13}$  TCR clonotypes [95]. In addition, the TCR may only recognize a specific region of a presented peptide (not all the amino acids are scanned – discontinuous epitopes), altering T cell recognition and activation [96,97]. Thus, the TCR can recognize

multiple epitopes (self and non-self), a phenomenon known as “poly-specificity” [98,99]. This also applies to antibodies, in which despite affinity maturation, it has been illustrated that mature antibodies tend to exhibit promiscuity (i.e., polyspecificity), despite the acquisition of a relatively rigid binding pocket [100–102].

Presumably, any given T cell receptor must react to many different epitopes to react with all or most antigens from environmental pathogens [98]. Mimotopes, which are macromolecules with a similar structure to antigen epitopes, can lead to antigenic mimicry, where similar antigens activate immune receptors causing the immune system to target both the primary antigen and the similar antigen [99]. However, why are only some individuals susceptible to ADs? According to Cusick et al. [103], three pathways of autoreactivity by molecular mimicry can occur: 1) “TCR, given the polyspecificity of this receptor, could recognize the microbe and self-antigens,” 2) “some T cells exhibit the presence of double TCRs on their surface. One TCR distinguishes the viral/bacteria peptides, and the other is reactive to self-peptides”, and 3) “the TCR is a chimera having two β chains and one α chain, or two α chains and one β chain, which, in different mixtures, may result in recognition of self-antigens or foreign peptides inducing the development of autoimmunity” (Fig. 1) [4,104].

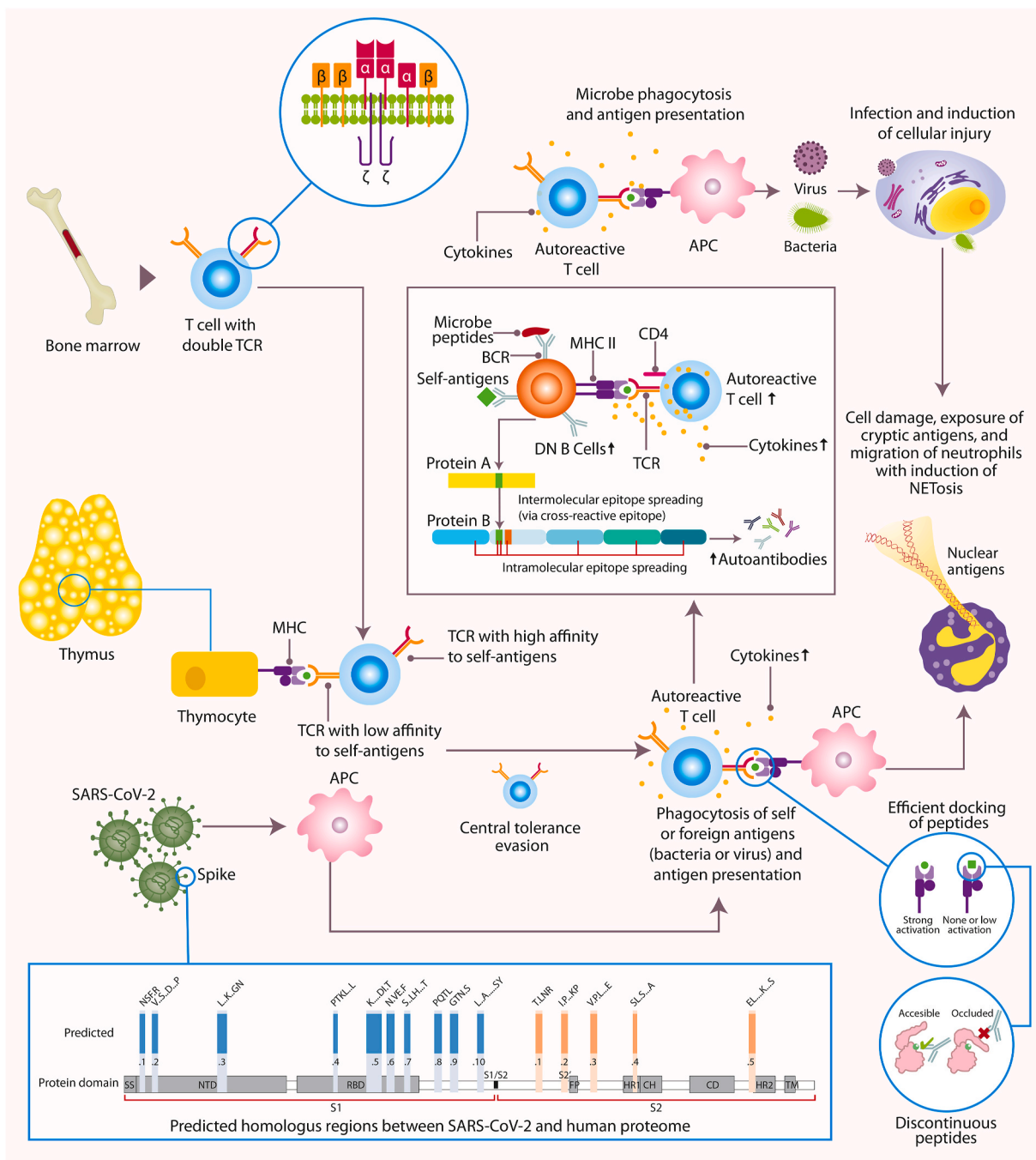
In humans, about 30% of T-cells have two functional TCR α chains, while in mice up to 15% of T-cells express more than one TCR α chain [105,106]. Additionally, 1% of T-cells in humans and mice express more than one TCR β chain [107,108]. Although the processes behind the existence of dual TCRs is not fully understood, defects in allelic exclusion in some T cells can confer them a survival advantage by enabling them to recognize a wider range of antigens, but it can also lead to autoimmunity [109,110]. In this context, the first evidence of the potential of double receptors in the development of autoimmunity following infection was provided by Libbey et al. [111], who demonstrated that a dual TCR was present on the surface of T-cells following infection by Theiler's murine encephalomyelitis virus (TMEV) in SJL/J mice which developed experimental autoimmune encephalomyelitis (EAE).

Homologous peptide structures (3D peptide conformation) rather than similar amino acid sequences are also implicated in T cell activation [112]. It was confirmed in experimental autoimmune uveitis (EAU) and EAE models that peptides with less than 50% similarity could induce T cell activation [113,114]. However, truncated peptides did not induce T-cell proliferation and could block the MHC II binding groove [115]. This data suggested that the peptide 3D structure and its fit into the binding groove of MHC and TCR are also critical for analyzing mimotopes.

The role of 3D structure in TCR recognition may be similar to antibodies, which recognize conformational and discontinuous epitopes rather than linear peptides (Fig. 1) [116]. Peng et al. [82] reported that anti-desmoglein (Dsg) antibodies in pemphigus foliaceus (PF) did not recognize linearized peptides in Dsg1 [117]. Interestingly, antigenic mimicry for Dsg1 was related to an antigen within the LMJ11 protein (a sand fly salivary gland antigen) [82]. The link between LMJ11 and endemic PF, also known as Fogo Selvagem (FS), has been identified in affected areas. The precise mechanisms by which this sand fly protein may enter the immune system and elicit antigenic responses remain unclear. Nevertheless, this model has yielded compelling evidence for its involvement in autoimmune processes [82].

In this model (i.e., FS), molecular mimicry resulted in intermolecular epitope spreading (ES), resulting in an initial autoimmune response against a cross-reactive epitope on Dsg1. Following ES in Dsg1, PF patients develop pathogenic anti-Dsg1 antibodies directed against the EC1 or EC2 domains, whereas autoantibodies arising from ES directed against the epitopes on the EC3, EC4, and EC5 domains of Dsg1 were not pathogenic [82]. This confirms that the initial humoral response might not be pathogenic despite the evidence of molecular mimicry, but it also implies that ES propagates humoral response in this condition (Fig. 1).

Antibody promiscuity refers to the ability of an antibody to bind to multiple different antigens or epitopes, rather than being specific to just



**Fig. 1.** Proposed mechanism for evasion of central and peripheral tolerance, and development of autoimmunity secondary to molecular mimicry (Taken and adapted from Refs. [4,104]). T-cells derived from the bone marrow may have a single or double TCR with various chain arrangements. This situation might help avoid central tolerance, which ultimately might help T-cells triggered by foreign or self-antigens presented by APCs to become activated. T-cell activation in this process may boost the formation of autoantibodies, or vice versa, since B-cells may present antigens to autoreactive T-cells, which may increase cytokine production and directly injure tissues through cytotoxicity. Activated B and T cells are implicated in the reactivity to self and foreign epitopes. Inter- and intramolecular epitope spreading diversifies the immune response and expands the production of autoantibodies against the initial antigen and other related proteins. SARS-CoV-2 harbors several mimotopes in the S protein. Such mimotopes could induce cross-reactivity and activation of B and T cells after APC antigen presentation. However, docking and affinity to TCR and HMC receptors may define further downstream activation of immune cells. Regarding immune receptors and antibodies, linear and non-linear epitopes defined by 3D structure could be implicated in affinity and avidity of interactions. APC: antigen-presenting cell; BCR: B-cell receptor; DN: Doble negative; MHC: major histocompatibility complex; S: Spike; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TCR: T-cell receptor.

one [100–102]. This means that a single antibody can recognize and bind to a variety of different molecules or structures. Antibody promiscuity is thought to be an important factor in the ability of the immune system to defend against a wide range of pathogens. By being able to recognize many different antigens, antibodies can help the immune system to mount a more effective response to a diverse array of threats

[100–102]. However, promiscuous antibodies can also have drawbacks. For example, if an antibody is too promiscuous, it may not be able to distinguish between harmful and harmless antigens, which could lead to autoimmune reactions or other unintended consequences [100–102]. Additional research is necessary to determine whether this phenomenon occurs in acute COVID-19 and PCS.

### 3. SARS-CoV-2 and autoimmunity

New-onset autoantibodies have been found in acute COVID-19 [85]. These autoantibodies are related to multiple ADs such as systemic sclerosis (SSc), myositis, systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), gastrointestinal, rheumatic, thyroid, and phospholipid autoimmunity [85,86]. In addition, analysis for other reactivities in acute COVID-19 demonstrated that patients exhibit IgG autoantibodies involved in the immune response, comprising effector function, lymphocyte activation, IFN response, and leukocyte trafficking [118]. Antibodies against Hypocretin Receptor 2 (HCRTR2) are the most relevant autoantibodies associated with the severity of disease during acute COVID-19 [118]. This receptor is located in the hypothalamus, and high levels of this autoantibody were correlated with lower Glasgow coma scale scores, suggesting a pathogenic role in the arousal state in infected patients.

In addition, latent autoimmunity (i.e., the presence of autoantibodies without the fulfillment of validated classification criteria for ADs [119]), including antinuclear antibodies (ANAs), thyroid peroxidase (TPO), rheumatoid factor (RF), and  $\beta$ 2-Glycoprotein 1 ( $\beta$ 2GP1) antibodies, influence the outcomes in hospitalized patients [86]. Autoimmunity to type I IFNs has also been implicated in mortality, possibly contributing to death in about 20% of COVID-19 deaths [87,120,121]. Auto-antibodies neutralizing type I IFNs predate SARS-CoV-2 infection [87]. Positivity for such autoantibodies has been associated with increased risk for herpes virus disease in critical COVID-19 [122]. Other anti-cytokine antibodies for IL-1, IL-6, IL-10, IL-12p70, IL-15, IL-17A, IL-22, IL-33, granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage inflammatory protein-1 $\alpha$  (MIP-1 $\alpha$ ) have also been described [118]. This is similar to other infectious disease such as mucocutaneous candidiasis and staphylococcal diseases which are associated with the presence of autoantibodies against IL-17A/F and IL-6, respectively [123].

In addition to type I IFNs antibodies, Fonseca et al. [124] demonstrated that patients with acute COVID-19 exhibit an age-associated increase in autoantibody levels against 16 antigens (i.e., Amyloid  $\beta$  Peptide,  $\beta$  Catenin, Cardiolipin, Claudin 5, Enteric Nerve, Epithelial Cell Antigen, Fibulin, Glutamic Acid Decarboxylase, Human Epidermal Keratin, Insulin Receptor, Islet Cell Antigen, Liver Microsomal Antigen, Platelet Glycoprotein, Transglutaminase 3, Transglutaminase 6, and Zonulin), and the autoantibodies targeting cardiolipin, claudin, and platelet glycoprotein were associated with the stratification of severe COVID-19 in elderly patients [124]. These results correlate with the initial reports of coagulopathy associated with antiphospholipid antibodies in critically ill patients with COVID-19 [86,125,126]. Other autoantibodies related to disease severity include those against angiotensin-converting enzyme 2 (ACE2) [127].

As a result of SARS-CoV-2 infection in children, a multisystem inflammatory syndrome in children (MIS-C) has been reported. The clinical manifestations of MIS-C include mucocutaneous manifestations resembling Kawasaki disease (KD), rash, edema, lymphadenopathy, and conjunctivitis [128,129]. Despite the clinical similarities between MIS-C and KD, Consiglio et al. [128] noted that MIS-C exhibits unique cytokine and lymphocyte phenotypes that differentiate both conditions. In addition, autoantibodies against MAP2K2, CSNK1A1, CSNK2A1, and CSNK1E1 may help to differentiate MIS-C from KD, thus suggesting that SARS-CoV-2 induced a differential immune response with the production of autoantibodies with diverse specificities.

#### 3.1. Molecular mimicry and SARS-CoV-2: antigenic sin?

Immune imprinting, also known as original antigenic sin, is the immune system's inclination to rely upon existing memory cells rather than initiate a de novo response when it encounters a novel but closely comparable antigen [130,131]. Preexisting-immunity, i.e., that has already developed, could boost crossreactive antibody responses to

epitopes shared by the current and previously encountered antigens [130,132,133]. In a recent analysis, patients with severe COVID-19 exhibited a shift in antibody response to the respiratory syncytial virus, cytomegalovirus (CMV), and herpes simplex virus-1 (HSV-1), thus suggesting a crossreactivity with the SARS-CoV-2 proteome [134]. Clinical trials for polio, influenza, measles-mumps-rubella, and Bacillus Calmette-Guérin vaccinations are testing the cross-protective effects of non-COVID-19 vaccines against SARS-CoV-2 with promising pre-publication findings [135].

As many autoantibodies in COVID-19 and PCS have a high pre-existing population prevalence, a question remains on defining the epitopes/mechanism within the SARS-CoV-2 proteome that leads to such emergence. A recent study by Jaago et al. [136] using a high throughput random peptide phage display method found 15 highly antigenic epitopes; ten on the S region 1 (S1) and five on S2 (Fig. 1). Epitopes between regions S1.4 to S1.7 correspond to receptor binding protein (RBD) which are commonly targeted by neutralizing antibodies during acute infection or those induced by vaccination [136].

In addition, IgG reactivity to the 15 S protein epitopes was found in pre-pandemic and acute COVID-19 sera. This is in line with the study by Quiros-Fernandez et al. [137], which found that multiple SARS-CoV-2 epitopes in S1 and S2 regions could induce activation of CD8<sup>+</sup> T cells of healthy pre-pandemic donors, including naïve, memory, and effector subsets. The finding that individuals have pre-existing immunity to some of the identified epitopes and that these epitopes can activate CD8<sup>+</sup> T cells of healthy unexposed donors suggests that prior exposure to related viruses or vaccination (i.e., immune printing) may contribute to the development of autoimmunity.

Further analysis confirmed that several S1 and S2 epitopes shared reactivity for common cold coronaviruses (e.g., SARS-CoV, OC43, and HKU) and other viral antigens from CMV, HSV-1, and Epstein-Barr virus (EBV) [136]. In addition, 63 human proteins with highly similar antigenic determinants to those within the 15 epitopes were identified in naïve (i.e., pre-pandemic) and COVID-19 patients. Those proteins were related to neuronal and cardiovascular development, Parkinson's disease, inflammatory bowel disease, synaptogenesis, chronic pulmonary disease, cancer, and periodontitis [136]. It demonstrates the molecular mimicry between SARS-CoV-2 and the human proteome, and evidenced IgG crossreactivity to previously recognized pathogenic targets in chronic conditions. Furthermore, the authors have shown that the existence of prior seroresponse to three specific epitopes of protein S (namely, S1.6, S1.8, and S2.1) could serve as an indicator for predicting the likelihood of exacerbated immunopathology associated with acute or chronic COVID-19 conditions [136].

#### 3.2. Predicted homologous peptides between human proteome and SARS-CoV-2 and predicted binding to adaptive immune receptors

In addition to the peptide homology between the human proteome and the SARS-CoV-2, it is important to define their binding affinity to adaptive immune receptors (i.e., TCR, B cell receptor [BCR], or MHC). In the study by Karami Fath et al. [30], using a bioinformatic approach, the SARS-CoV-2 proteome was used to generate all 8- to 12-mer possible peptides, yielding a total of 48,530 peptides. The choice of peptide length was influenced by the need to balance sensitivity and specificity in their analysis. Longer peptides may be more specific to a particular antigen, but they may also miss other potential targets, while shorter peptides may be more sensitive but less specific. The choice of 8- to 12-mers allows for a balance between sensitivity and specificity, while also enabling the identification of potential targets for both MHC class I and class II molecules.

From the studied peptides, 23 SARS-CoV-2 peptides exhibit exact matches in the human proteome (18 in the ORF1ab polyprotein region, one in the non-structural protein 7a [NS7a], two in the surface glycoprotein, and two in the envelope protein), and all the matching peptides were from the octamer library [30]. Most of these peptides are

ubiquitous and expressed in most tissues. However, some exhibit high specificity for the brain, heart, skeletal muscle, liver, pancreas, placenta, kidney, lungs, colon, peripheral blood, testis, endometrium, and hair follicles [30].

Next, from these SARS-CoV-2 peptides, only the ESGLKTIL (binds to HLA-B\*08:01), EVLLAPLL (binds to HLA-B\*51:07), NVAITRAK (binds to HLA-A\*34:02), RYPANSIV (binds to HLA-A\*24:02, HLA-A\*24:03, HLA-A\*24:07, HLA-C\*14:02, and HLA-C\*14:03), RRSFYVYA (binds to HLA-B\*27:02, HLA-B\*27:03, HLA-B\*27:04, and HLA-B\*27:05), and RFNVAITR (binds to HLA-A\*33:03 and HLA-A\*74:01) were predicted to bind to HLA proteins. Based on previous studies, they might induce immunogenic activity [30]. These results are similar to those from Adiguzel et al. [138], who found, by bioinformatic analysis, that mimicry between SARS-CoV-2 NSP6 with the CRB1 isoform I precursor could be associated with autoimmunity *via* the interaction with HLA\*A02:01 and HLA\*A24:02.

Both studies may have only identified binding peptides for MHC class I molecules because of the length of the peptides they used. It is possible that longer peptides, more representative of MHC class II binders, may reveal additional potential targets for T cell responses. However, it is also possible that the SARS-CoV-2 virus has a greater potential to induce autoimmune responses through MHC class I pathways, or that the MHC class I binders identified by the studies are the most relevant targets for T cell responses against the virus. Additional studies would be needed to investigate this further and to determine the extent to which the identified peptides could induce autoimmune responses (e.g., animal models, tetramer assays, or antibody cross reactivity studies).

Interestingly, when examining the Omicron variants (i.e., 21 K and 21 L), the molecular mimicry-associated risk appeared to be associated with HLA-A\*24:02 and HLA-B\*27:05 upon infection with Omicron 21 L. In addition, other Omicron peptides were possible binders to the HLA-B\*27:05 and HLA-A\*01:01 haplotypes, whereas the binding to HLA-B\*07:02 could have been lost or diminished [138]. It is important to note that the authors of such study used bioinformatic methods to analyze the SARS-CoV-2 proteome and predict the potential binding of viral peptides to MCH molecules. This suggests that the emergence of new SARS-CoV-2 variants could shift the risk for autoreactivity to different HLA alleles associated with different ADs. Nevertheless, further experimental, and epidemiological evidence is required to confirm these results.

### 3.3. Peptide modeling, molecular docking, and affinity of homologous peptides

In addition to predicted HLA binding, peptide modeling and molecular docking (i.e., affinity and orientation) are critical for determining truly immunogenic peptides associated with molecular mimicry. Using HLA 3D structures and matching the corresponding binding peptides, Karami Fath et al. [30] found four SARS-CoV-2 candidate homologous peptide sequences for peptide modeling (i.e., ESGLKTIL, RYPANSIV, NVAITRAK, and RRARSVAS). These peptides are binders for HLA-B\*08:01, HLA-A\*024:02, HLA-A\*11:01, and HLA-B\*27:05, respectively.

Bioinformatic docking analysis demonstrated that all the peptides strongly interacted with the experimentally confirmed HLA molecules. This confirmed that besides their sequence homology to human proteome, the peptides would also be able to strongly interact with their matching HLAs. These HLAs have been previously associated with rheumatoid arthritis (RA), rheumatic carditis, Crohn's disease, ankylosing spondylitis, type 1 diabetes (T1D), and multiple sclerosis (MS) [30].

The frequency of expression of particular HLA alleles varies considerably across different ethnic groups [139]. Estimating the frequency of optimal peptide binding to different sets of HLA alleles (i.e., population coverage analysis) helps to define the probability of immunogenic response in different geographic regions [140,141]. In the analysis of

population coverage for selected SARS-CoV-2 peptides, RYPANSIV (world coverage 25.74%), NVAITRAK (world coverage 15.53%), ESGLKTIL (world coverage 10.55%), RRSFYVYA (world coverage 7.33%), and RFNVAITR (world coverage 6.91%) were the top covered peptides [30]. In addition, over 57% of the world's population was calculated to be covered by all peptides with anticipated HLA binding. The regions with the most prominent population coverage were Oceania (80.72%), East Asia (83.78%), and Southeast Asia (84.12%) [30].

### 3.4. Animal models, SARS-CoV-2, and autoimmunity

The research conducted by Shen et al. [142] involved the inoculation of SARS-CoV-2 into K18-hACE2 mice, resulting in a significant decrease in saliva flow rate, augmented levels of ANAs against SS-B/La, and notable lymphocyte infiltration in both the lacrimal and salivary glands resembling a SS-like phenotype. In the context of COVID-19 patients, the analysis of serum samples indicated a notable elevation in ANAs, anti-SSA/Ro52, and anti-SSB/La. Examination of minor salivary gland biopsies obtained from convalescent COVID-19 patients revealed the presence of focal lymphocytic infiltrates focus scores >2 [142]. This is the first experimental evidence of an autoimmune-like phenotype induced by SARS-CoV-2 *in vivo* and correlates with pathology in humans.

This study adds to the growing consensus that molecular mimicry drives SARS-CoV-2-induced autoimmunity: 1) there is evidence of homology between the human proteome and the SARS-CoV-2.2) studies confirm that patients with COVID-19 exhibit autoantibodies against both epitopes in humans and the infectious agent, and crossreactivity was noted in samples from pre-pandemic acute infected patients. 3) An epidemiological association exists between SARS-CoV-2 and the development of autoimmunity, including its role in mortality. 4) Inoculation with SARS-CoV-2 into K18-hACE2 mice is associated with SS-like phenotype. However, further studies providing evidence on additional animal models, as well as longitudinal cohorts in humans, could provide definitive evidence of molecular mimicry in the development of autoimmunity by SARS-CoV-2.

### 3.5. Immunological mechanisms of autoimmunity in acute COVID-19

Similar to SLE, extrafollicular B cell (EFB) activation is evident in patients with COVID-19, and this causes an expansion of the B cell repertoire's antibody-producing cells [143]. In critically ill COVID-19 patients, the IgD<sup>-</sup>CD27<sup>-</sup> (double negative [DN2]) population of effector B cells expands and is one of the main causes of an inappropriate humoral response (i.e., high production of anti-SARS-CoV-2 antibodies but worse clinical outcomes and a stronger pro-inflammatory state) [143]. In inflammatory disorders like COVID-19 and SLE, the DN2 B cells, which mostly evolve in the EF pathway, tend to move to inflammatory tissues and produce autoantibodies [143,144].

The immune response to SARS-CoV-2 is associated with TLR3 and TLR7 RNA sensor pathways [145], and this pattern recognition receptor (PRR) has a similar role in the pathogenesis of SLE and COVID-19-associated autoimmunity through the induction of DN2 autoreactive or age-associated B cells (ABCs) [143,146]. TLR7 is critical for recognizing single-stranded RNA (ssRNA) from both viral and non-viral sources in the endosomes and induces the production of IFNs. In SLE, it was found that the *TLR7<sup>Y264H</sup>* variant confers an increased risk for the development of autoimmunity through a gain of function mutation [147]. Given that SARS-CoV-2 has the potential to activate DN2 autoreactive cells, potentially via a TLR7 mechanism (analogous to SLE) [143, 146], it is probable that this may result in the generation of autoantibodies with varying specificities. This could be counterintuitive to the fact that 10% of patients with critical COVID-19 exhibit anti-IFN antibodies (which are associated with a impaired response to the virus). However, such autoantibodies are only present in a small number of patients; thus, the activation of DN2 cells by this stimulus is possible in most infected patients.

In addition, another potential source of autoantibodies includes neutrophil extracellular traps (NETs). The inflammatory response to gram-positive and gram-negative bacteria is mediated by NETs, an interconnected network of granule proteins and chromatin produced by neutrophils [148]. Notably, while NETs are known to be generated in response to non-viral stimuli, it is worth mentioning that viral infections can also trigger the formation of NETs albeit to a lesser degree [149]. These NETs constitute a significant source of cryptic antigens that promote the formation of antibodies, especially against nuclear antigens (Fig. 1).

In COVID-19, NETs are recognized to play a critical role in inflammation and thrombosis, and they induce the production of anti-phospholipid antibodies [150,151], and circulating NETs correlate with disease severity [152–155]. In this line, anti-NET antibodies likely impair NET clearance and may potentiate SARS-CoV-2-mediated thromboinflammation [151]. Additional hypotheses suggest that anti-phospholipid antibodies could potentiate NETs formation, by promoting the interaction between platelets and neutrophils with the consequent neutrophilic activation and B cell activating factor (BAFF) production, a release that could perpetuate and potentiate autoantibody production by autoreactive B cells [126].

Epitope spreading is the diversification of the immune response from the initial dominant epitope-specific immune response to subdominant epitopes on the same protein (intramolecular ES) or other autoantigens (intermolecular ES) (Fig. 1) [156,157]. This phenomenon has been extensively studied in MS, T1D, and myasthenia gravis [158]. In MS, immunization with a proteolipid protein (PLP)<sub>139–151</sub> peptide in SJL mice induces the development of EAE within three days. However, new antigenic epitopes emerge during the subsequent relapses, such as PLP<sub>178–191</sub>, and for other proteins, such as myelin basic protein (MBP)<sub>84–104</sub> [159]. This exemplified the role of mimotopes in autoimmunity and the diversification of the immune response with pathogenic potential. A recent bioinformatic analysis found that predicted epitopes from SARS-CoV-2 and crossreactive with PARP14 could be a source of intermolecular ES. This protein had the second-largest number of projected cross-reactive MHC-II ligands, the most expected cross-reactive MHC-I, and the highest number of predicted cross-reactive conformational B-cell epitopes [160].

Overall, evidence suggests that autoimmunity induced by COVID-19 could be associated with molecular mimicry to epitopes in the S1 and S2 SARS-CoV-2 regions, the production of autoantibodies secondary to increased NETosis, expansion, and activation of effector B cells, or epitope spreading leading to the production of autoantibodies with diverse specificity. In addition, the cytokine storm induced in the early stages of the infection also promotes the activation of inflammatory pathways that could be associated with a non-specific immune response giving it a higher potential to induce autoimmunity over other viruses. This evidence may explain the plethora of autoantibodies found during acute COVID-19 and PCS, in which patients present positivity for autoantibodies but lack, most of the time, the fulfillment of classification criteria for new-onset ADs. However, the evidence of thrombosis, rheumatological manifestations, and organ compromise associated with autoantibodies during acute COVID-19 suggest their pathogenic role in the acute disease and highlight the possibility of the development of overt autoimmunity during PCS and beyond.

Compared to Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-1, SARS-CoV-2 appears to have a higher incidence of autoimmune phenomena, but the exact reasons for this difference are not yet fully understood. The structural similarities between some of the SARS-CoV-2 proteins and human proteins may contribute to the development of autoimmunity to a greater extent compared to MERS-CoV and SARS-CoV-1. Additionally, SARS-CoV-2 may be able to evade the immune system more effectively than the other two viruses, leading to a more sustained and robust inflammatory response that could contribute to the development of autoimmune phenomena. However, further studies are needed to fully understand the mechanisms underlying the

increased incidence of autoimmunity in COVID-19 compared to other coronaviruses.

#### 4. Post-COVID syndrome, autoinflammation, and autoimmunity

Kastner et al. coined the term “autoinflammatory” in 1999 to describe two entities with episodes of recurring inflammation defined by fever but no indication of infectious diseases [161]. The conditions were familial Mediterranean fever and TNF receptor-associated periodic syndrome [162,163]. Since then, more than 30 autoinflammatory entities with various pathophysiological mechanisms have been described. Overactivation of inflammation (mainly related to type I IFNs) and lack of inhibition in several signaling pathways, notably nuclear factor- $\kappa$ B (NF- $\kappa$ B), are the fundamental causes of these disorders [163,164].

The difference between ADs and those considered “autoinflammatory” lies in the type of immune response. T and B cells are autoreactive against specific antigens in autoimmune conditions. In contrast, in autoinflammatory diseases, there is no specific adaptive autoreactivity, rather over-activation of innate immune pathways. The predominance of the immune response is determined by the activation of signaling pathways mainly related to the production of IL-1 $\beta$  and IFN- $\alpha$  [161,165].

PCS's most notable clinical manifestations include musculoskeletal, respiratory, digestive, and neurological manifestations (e.g., depression, myalgic encephalomyelitis/chronic fatigue syndrome – ME/CFS) [166]. One out of three patients may present with these four clinical components. Noteworthy, PCS is not associated with the severity of acute illness [166]. The mechanisms underlying PCS are enigmatic. Evidence for endotheliopathy [167], viral persistence [168], endocrine dysregulation [169], autoimmune response [170], and chronic inflammatory state [171] has been provided. Nevertheless, there is evidence that PCS occurs between two main spectrums: autoimmune and autoinflammatory. Patients with PCS exhibited abundant DN2 B cells, CD8<sup>+</sup> T cells, Th1, and Th17 cytokines after 3–6 months of recovery, indicating a hyperinflammatory milieu. Furthermore, patients had decreased B cell response due to IL-6/IL-10 imbalance [172] and elevated TNF and IL-1 [173].

Longer follow-ups (up to 11 months) suggest that this inflammatory phenotype persisted over time. We and others observed an increase of pro-inflammatory cytokines in PCS (i.e., IFN- $\alpha$ , TNF- $\alpha$ , G-CSF, IL17A, IL-6, IL1- $\beta$ , and IL-13) [88,174,175]. Furthermore, in terms of the cellular immune response, significant components of cellular immunity in PCS patients did not return to normal baseline 7–9 months after SARS-CoV-2 infection [88]. There were an increase in CD4<sup>+</sup> effector memory T cells, CD8<sup>+</sup> effector T cells, Th9 cells, and naïve B cells [88]. Similar findings were reported by Phetsouphanh et al. [175] who assert that SARS-CoV-2 infection has long-lasting impacts on the innate and adaptive immune systems (8 months after infection). It led to an inflammatory state characterized by elevated levels of type I IFN (IFN- $\beta$ ) and type III IFN (IFN- $\lambda$ 1) and elevated levels of activated and exhausted immune cells.

Additionally, PCS has been linked to long-lasting changes in innate (NK cells, LD neutrophils, and CXCR3<sup>+</sup> monocytes) and adaptive (helper T cells, follicular T cells, and regulatory T cells) immune responses [176]. In a longer follow-up (24 months), Schultheiß et al. [177] found that 60% of patients with mild COVID-19 reported PCS, and they exhibited increased levels of IL-1 $\beta$ , IL-6, and TNF $\alpha$ , which may be released by overactive monocytes and/or macrophages. In conclusion, individuals with PCS have defective innate and adaptive immune responses, which suggests that the clinical symptoms of this condition are at the crossroad of autoinflammation and autoimmunity [90].

It is important to note that SARS-CoV-2 is not unique in its ability to produce post-viral symptomatology after acute infection. Musculoskeletal symptoms are a frequent manifestation following the resolution of acute viral infections and have been reported with other viral infections as well. Notably, hepatitis C and endemic alphaviruses, such as Ross River, Barmah Sindbis, Chikungunya, Forest, Mayaro, and O'nyong-

nyong viruses have been implicated in the development of chronic arthritis. In contrast, coronaviruses (i.e., MERS-CoV and SARS-CoV-1) typically result in arthralgia and myalgias, rather than chronic arthritis [178].

In addition, it has been observed that post-viral syndromes typically last for a duration of approximately six months [179]. However, in some cases, patients continue to experience persistent symptoms beyond this timeframe. This is particularly true in the case of PCS, which has been documented to persist for longer than one year in some patients [166]. The persistence of sequelae following COVID-19 infection appears to differentiate it from other viral infections, where symptoms tend to be transitory. In some cases, the prolonged presence of symptoms associated with COVID-19 can even give rise to overt autoimmune disorders. These observations underscore the unique nature of COVID-19 in its ability to trigger a protracted and potentially chronic disease course and emphasize the importance of continued research into the pathophysiological mechanisms underlying this condition.

The management of PCS focus on the treatment of coexisting conditions, as well as the optimization of organ-specific compromise [180, 181]. However, similar to ADs, the administration of short-term glucocorticoids may ameliorate and reverse PCS [182]. In the former study, Utrero-Rico et al. [182] found that patients with PCS treated with a 4-day course of corticosteroids (prednisone, 30 mg/day) exhibited a reversal of Th1-predominance, augmentation in naïve and regulatory T cells, and decrease of the PD-1 exhaustion marker, and it was maintained after 4-month follow-up. On the other hand, given the evidence of persistent elevated levels of cytokines during PCS (e.g., TNF- $\alpha$ , IL-6, and IL-1 $\beta$ ) [88], the study of anti-cytokine therapy warrant further attention. Such therapies may have a significant effect on the persistent inflammatory state of PCS that is associated with clinical phenotypes.

#### 4.1. Persistent latent autoimmunity following acute COVID-19

Autoantibodies persist after acute COVID-19, and latent PolyA increased over time in PCS (i.e., new-onset autoantibodies after infection) [88]. We demonstrated that latent autoimmunity (at least one positive autoantibody) and PolyA (more than one positive autoantibody) are found in 83% and 62% of PCS patients, respectively [183]. The most prevalent IgG autoantibodies (>10% for each antigen) were those against IL-2, CD8B, and thyroglobulin (Tg), with anti-IFNs being identified in 5–10% of individuals [183]. Moody et al. [184] confirmed our results in patients with PCS using a similar technique in a distinct cohort. They found that after eight months of recovery, the most prevalent IgG autoantibodies were against Calprotectin, CD4,  $\beta$ 2GPI1, IFN- $\alpha$ 2, RNP/Sm, CENP-B, U1-snRNP-68, IFN- $\alpha$ , PM/Scl75, Vitronectin, Histone, IFN- $\beta$ 1, and SmD (>10% for each antigen). Interestingly, the positivity for Calprotectin was associated with better clinical outcomes in PCS.

In the same line, Lingel et al. [185] demonstrated that PCS patients exhibit persistence of latent autoantibodies for cyclic citrullinated peptides and anti-tissue transglutaminase up to 4–8 months of recovery. Antiphospholipid antibodies have also been described in patients with PCS [186,187]. Liu et al. [188] demonstrated a correlation between autoantibodies and the IgG immune response to SARS-CoV-2. This is consistent with our results in which autoantibodies highly correlated with anti-SARS-CoV-2 S1, S2, and RBD antibodies [183]. As explained above, Jaago et al. [136] found immune imprinting to S1 and S2 epitopes. In this line, the findings that levels of autoantibodies correlate with SARS-CoV-2 antibodies for S and RBD suggest that this phenomenon also takes place during the convalescent phase of the disease, supporting a persistent immune activation with repercussions on autoimmunity.

The spectrum of PCS includes neurological manifestations such as ME/CFS. Patients with mild to moderate acute COVID-19 who developed PCS exhibited high levels of antibodies targeting G-protein coupled receptors, and antibodies for ADRB2, STAB1, and ADRA2A were the

strongest classifiers for PCS outcomes [189]. These autoantibodies correlate with the severity of symptoms and autonomic dysfunction measured by the Composite Autonomic Symptom Score 31 (COMPASS-31). These results resemble our previous results on autonomic function measured by COMPASS-31 as a classifier of the severity of PCS [166]. In addition, it suggests the role of autoantibodies in clinical phenotypes, likely through the production of de novo autoantibodies or the immune imprinting to previously recognized peptides *via* molecular mimicry.

Other autoantibodies have also been associated with symptom persistence after acute COVID-19. Son et al. [190], found that patients with PCS exhibited higher detectable ANAs three months after recovery (43% of total reactivities), with U1-snRNP and anti-SS-B/La antibodies associated with fatigue and dyspnea. Other autoantibodies were also found against ACE2, MDA5, CD255, SS-B/La, and PM/Scl-75. Interestingly, up to 30% of patients with reactivity to SmD1, PCNA, SSA/Ro60, SS-B/La, U1-snRNP, PMScl, Ku, and DFS70 remained positive after 12 months post-recovery. In addition, there were 12% of de novo reactivities after recovery, suggesting the formation of new-onset autoantibodies during this time [190].

The main drawback to confirming the relationship between SARS-CoV-2 and autoimmunity (i.e., causality) is the lack of individual patient data before the pandemic and may hinder the evaluation of latent autoimmunity following SARS-CoV-2 infection (See below section 4.2). Su et al. [191] suggested that many autoantibodies may be present before the onset of the disease, and such autoantibodies could be associated with the emergence of PCS. However, the clinical implication of such autoantibodies is unclear. Evidence indicates that latent autoimmunity may precede the appearance of ADs several years before clinical manifestations (i.e., overt autoimmunity), and several random factors are required for its emergence (e.g., environmental and genetics) [192]. It highlights the critical role of longitudinal studies in PCS to confirm the development or not of overt autoimmunity in the incoming years.

#### 4.2. Overt autoimmunity following acute COVID-19

We have reported that 3% of patients clinically develop overt autoimmunity after eight months of follow-up [183]. Overt autoimmunity was characterized by SLE, Hashimoto's thyroiditis, and polymyositis. Additional case reports on autoimmune encephalitis [193], SLE [194, 195], giant cell arteritis [196], Graves' disease [197], vasculitis [198, 199], transverse myelitis [200], idiopathic inflammatory myopathies [89], SSc [201], and adult-onset Still's disease [89] have also been reported. A summary of possible autoimmunity and autoinflammation following acute COVID-19 is found in Table 2 [194,195,197,201–243] [244].

A retrospective cohort study including around 4 million patients in the United States (888,463 cases and 2,926,016 controls) demonstrated that COVID-19 patients have higher odds of developing RA, SLE, ankylosing spondylitis, dermatopolymyositis, SSc, SS, mixed connective tissue disease, Behçet's disease, polymyalgia rheumatica, vasculitis, psoriasis, inflammatory bowel disease, celiac disease, and T1D [245]. It is tempting to speculate that patients who exhibit overt autoimmunity already had autoantibodies before acute COVID-19 since it may take many years for latent autoimmunity to become overt autoimmunity. Two additional matched cohort studies (still published as preprints) reported that SARS-CoV-2 infection is associated with an increased risk of developing new-onset autoimmune diseases after the acute phase of infection when compared with non-infected patients [246,247]. Thus, SARS-CoV-2 could accelerate the onset of autoimmunity. However, at the same time, acute COVID-19 could play a critical role in developing new-onset autoantibodies [85] and PCS [88].

### 5. Vaccination, SARS-CoV-2, and autoimmunity

Individuals receiving vaccines may rarely develop ADs. However,

**Table 2**  
Autoimmune diseases possibly triggered by SARS-CoV-2.

Autoimmune/Autoinflammatory Diseases	References
Alopecia areata	[202,203]
Ankylosing spondylitis	[204]
Antiphospholipid syndrome	[205–207]
Autoimmune encephalitis	[208]
Autoimmune hemolytic anemia	[209–211]
Autoimmune limbic encephalitis	[212]
Autoimmune thyroid disease	[213,214,219]
Celiac disease	[215]
Graves' disease	[197]
Guillain-Barré syndrome	[216–218]
Immune thrombocytopenic purpura	[220,221]
Inflammatory bowel disease	[222]
Miller-Fisher syndrome	[223–225]
Multiple sclerosis	[226–228]
Myasthenia gravis	[229]
Dermatomyositis	[230]
Polyneuritis cranialis	[224]
Polymyalgia rheumatica	[245]
Postural orthostatic tachycardia syndrome	[231,232]
Psoriatic arthritis	[233]
Psoriasis	[245]
Rheumatoid arthritis	[234,235]
Systemic lupus erythematosus	[194,195,236]
Systemic sclerosis	[201]
Type 1 diabetes mellitus	[237–239]
Vasculitis (i.e., Behcet's and Kawasaki)	[240,241]
Viral arthritis	[242,243]
Reactive arthritis	[244]

there is controversy about whether this is truly caused by vaccination or simply appears after vaccination as a coincidence [248]. Nearly 30.5 million doses of the AS03-adjuncted A (H1N1) vaccine were distributed after a pandemic linked to the H1N1 strain [249]. This high number of doses distributed in a short time allowed the study of several adverse events associated with autoimmunity (e.g., narcolepsy, Guillain-Barré syndrome-GBS). There was an approximately 3-fold increased risk for GBS after vaccination following immunization with the H1N1 Influenza vaccine [250]. This has been attributed to the similarity between some influenza virus structural proteins and those found in myelin sheaths [29].

Narcolepsy is characterized by an excessive daytime sleepiness accompanied by impaired nocturnal sleep and hallucinations [251]. Although the pathogenesis of this disease is not clear, susceptibility with the inheritance of the MHC class II DQB1\*06:02 gene, and the appearance of narcolepsy in mice injected with antibodies of narcoleptic patients, argue for a role of autoimmunity [252,253]. There was a significant increase in narcolepsy diagnosis after systematic vaccination with the AS03 vaccine in a population of Beijing, China. In 2015, Ahmed et al. [75] identified homology between the surface-exposed influenza nucleoprotein A and the extracellular domain of human HCRTR2, which are considered targets in the development of narcolepsy. In addition, antibodies derived from patients vaccinated with the pandemic Flu-vaccine demonstrated crossreactivity with these two structures. Thus, molecular mimicry appears to be one key factor in the development of narcolepsy secondary to the administration of the vaccine. These are just a few examples of vaccines associated with the development of overt ADs; other vaccines include those for hepatitis B virus (HBV) [254–260] and human papillomaviruses (HPV) [77,78,261–264] (Table 1).

We conducted a meta-analysis of 928 case reports on the new onset and relapsing ADs following COVID-19 vaccination [90]. The majority were women (53.6%), with a median age of 48. The most common event was new-onset conditions in 81.5% of the cases. Myocarditis, immune thrombocytopenia, and GBS were the three most prevalent illnesses linked to new-onset events after vaccination. On the other hand, immune thrombocytopenia, psoriasis, IgA nephropathy, and SLE were the

most prevalent conditions linked to relapse episodes. Interestingly, the first dosage was linked with new-onset events, whereas the second dose was related to the relapsing disease, and the events were presented after seven days of inoculation. Both new onset and relapsing ADs occurrences were linked to the mRNA-1273 SARS-CoV-2 vaccine, followed by Sinovac-CoronaVac and ChAdOx1 nCoV-19 vaccine (AZD1222) [90]. Whilst it is not possible to draw epidemiological causation from individual case reports, the findings of this meta-analysis may offer novel insights into the potential association between vaccination and autoimmunity. To establish a more conclusive relationship, further observational cohort studies are warranted.

As previously specified, the crossreactivity between SARS-CoV-2 proteome and other viruses could be related to vaccine efficacy but also implicated in developing new-onset autoimmunity or boosting pre-existing latent autoimmunity. The latter was demonstrated by Jaago et al. [136], in which pre-existing IgG reactivity to human proteins was associated with crossreactivity to S1 and S2 SARS-CoV-2 epitopes (See section 3.1). It has implications for vaccine development since cross-reactive epitopes in naïve individuals should be considered in their design [136]. These regions are essential since they contain the RBD, the vaccine target for viral neutralization.

The BNT162b2 and mRNA-1273 vaccines have the same sequence for S protein. Some regions in their sequences differ from the native S SARS-CoV-2 protein to enhance the ability to induce protein production, but most of them correspond to synonymous changes [265]. When examining the S sequence, both vaccines contain the RRARSVAS peptide, which strongly binds to the HLA-B\*27:05 allele, an HLA associated with autoimmunity, with a population coverage below 6% [30]. This suggests that vaccines harbour peptides that could induce autoreactivity in susceptible individuals, but the risk is low.

A neutralizing B-cell epitope of the SARS-CoV-2 surface glycoprotein contains the RRARSVAS peptide [266]. This peptide is close to the motif that gives the S protein its superantigenicity. The S SARS-CoV-2 T-cell epitopes contain this peptide sequence as well. These T-cell epitopes have been shown to bind to various HLAs, including those HLA-B\*08:01 and HLA-B\*07:02 linked to ADs [267]. It is also known that the DEDDSEPV binds to several HLAs, including those linked to ADs (i.e., HLA-B\*27:05 and HLA-C\*08:01) [268]. In addition, the S1 and S2 subunits discovered by Jaago and collaborators [136] are conserved in these vaccines (i.e., BNT162b2 and mRNA-1273), thus suggesting that these regions could be related to the emergence of latent autoimmunity or acceleration of overt autoimmunity onset after vaccination via molecular mimicry. This evidence is homologous to Sinovac-CoronaVac and AZD1222 vaccines, which harbor the highest reported frequency of overt autoimmunity following vaccination and exhibit the same S peptide sequence [90].

Although there have been sporadic reports of ADs developing following COVID-19 vaccination, it should be emphasized that such occurrences are infrequent and that the benefits of vaccination substantially outweigh any risks. Nevertheless, continuous monitoring of the vaccine's safety and the identification of any potential side effects is crucial. This is of particular importance, given the intricate web of environmental factors associated with ADs development, which renders the determination of causation complex. Consequently, more research is needed to better understand the relationship between COVID-19 vaccination and the development of ADs.

## 6. Conclusions

Molecular mimicry is the most suspicious culprit incriminated into the pathophysiology of autoimmunity in the time of COVID. Further studies confirming evidence on animal models, as well as confirmation of longitudinal cohorts in humans, will provide definitive evidence of molecular mimicry in the development of autoimmunity by SARS-CoV-2. The mechanisms underlying molecular mimicry-based cross-reactivity are intricate and incorporate both genetic and environmental

factors. Tridimensional structure, molecular docking, and affinity for pathogenic HLA peptides are new factors in the study of molecular mimicry. These new approaches and techniques will provide further information for optimal vaccine development in the current pandemic and those to come.

### Author contributions

MR, MH, CRS, PSCL, JMA, WMR, and MEG wrote, reviewed, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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