Myosin 16 mimicries may explain post- COVID-19 related neurological consequences

Ali Şahin[1], Huseyn Babayev[1], Fatıma Hacer Kurtoğlu[2], Seval Kübra Korkunç[3], Hilal Taşkıran[4], Celalleddin Bahadır Şanlıoğlu[2], Ahsen Morva Yılmaz[5], Kemal Erol[1], and Hasibe Artaç[1]

[1]Selcuk University Faculty of Medicine
[2]Silicosome Bioinformatics
[3]Koç University Institute of Health Sciences
[4]Max Planck Institute for Heart and Lung Research
[5]Biomedical Technology

May 19, 2023

Abstract

Autoimmune diseases arise from an immune response against self-antigens, but their pathophysiology is not fully understood. One of the proposed mechanisms is molecular mimicry, where infectious agents share similar antigens with host proteins leading to cross-reactivity. Our study aimed to investigate the presence of molecular mimicry between SARS-CoV-2 and human proteome using bioinformatics techniques. To accomplish this, we constructed sequences of 8 consecutive amino acids for structural proteins of SARS-CoV-2, such as spike, nucleocapsid, membrane, and envelope proteins. Next, we evaluated the mimicry of these sequences with the human proteome and analyzed their antigenicity, allergenicity, toxicity, TAP affinity, and IFNγ and IL-10 induction.We also calculated the affinity of the amino acid sequence DEDDSEPV, which showed molecular mimicry, to HLA receptors and found that it had a good binding energy. Based on our *in silico* analysis, we found that DEDDSEPV amino acid sequence might trigger autoimmunity due to its similarity with myosin-16 protein. Our study provides evidence for the possibility of SARS-CoV-2 inducing autoimmunity via molecular mimicry. Our findings can have significant implications for understanding the pathophysiology of autoimmune diseases and may contribute to the development of potential therapeutic strategies.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a viral infectious agent that broke out in Wuhan, China, and rapidly spread from China to the world [1,2]. SARS-CoV-2 causes Coronavirus disease

2019 (COVID-19) and postinfectious syndromes [3]. On 11 March 2020, the World Health Organization (WHO) declared the COVID-19 pandemic [4]. Flu-like symptoms, such as fever, fatigue, dry cough, headache, as well as myalgia, sore throat, nausea, and diarrhea, were reported and considered as clinical presentations of COVID-19 [5]. The SARS-CoV-2 virus belongs to the *beta-coronaviridae* genus [6]. It is a single-stranded RNA virus and has a spherical morphology. Also, it has four structural and sixteen non-structural proteins [7]. SARS-CoV-2 infects cells via splitting the spikes protein into S1 and S2 by TMPRSS8. S1 binds to the ACE-2 receptor, and S2 ensures the fusion of the virus into the cell [8]. When the virus enters the cell, it activates pattern recognition receptors (PRRs), which results in the release of proinflammatory cytokines from the infected cell, leading to macrophage activation [9]. Activated macrophages secrete cytokines and chemokines, leading to vasodilation and increased capillary permeability [10,11]. The alveoli are compressed by the passage of plasma into the interstitial space. This process also disrupts surfactant synthesis in alveolar type 2 cells in the lung. As a result of these pathological processes, alveolar collapse develops in the lung, and gas exchange is impaired [12]. IL-1, IL-6, and TNF, which are pro-inflammatory cytokines released into the blood, reach the hypothalamus via the blood and cause fever [13]. In several cases of COVID-19, the shortness of breath caused hypoxemia [14,15]. Critical patients develop septic shock and hypoxemia-related multi-organ dysfunction [16]. Hypoxia, which occurs with the development of pneumonia, causes tachycardia by activating the sympathetic system. The abnormal immune response can cause septic shock and death [17]. In short, due to pneumonia, vasodilation that decreases effective blood volume (BV) and peripheral resistance (PR) can lead to hypotension, reduced perfusion rate of the heart, and multi-organ failure [18]. In COVID cases, severe and critical patients show immune dysregulation [19], elevated inflammatory markers [20], low number regulatory immune cells [21], high-level inflammatory Th-17 cells [21], and neutrophils [22]. Medications used in autoimmune diseases, such as tocilizumab [23] and tofacitinib, are also used in COVID-19 patients [24]. Some autoantibodies were detected in COVID-19 patients [25]. It is thought that the immune dysregulation and hyperinflammatory state in COVID-19 can cause autoimmunity [26]. Viruses can cause Type II hypersensitivity reactions, including tissue damage caused by autoantibodies secondary to viral infections and inflammation. The aim of our study is to identify molecular mimicry between SARS-CoV-2 and the human proteome. We will also determine the immunological properties of sequences with molecular mimicry using immunoinformatics techniques.

Molecular mimicries and viral infections

Diseases that recognize host antigens as foreign and develop an immune response against our own antigens are called autoimmune diseases [27]. The etiopathogenesis of autoimmune diseases is still not fully explained, but environmental and genetic basis play a serious role in the clinical course of autoimmune diseases and the formation of the disease [28]. While the host's genetic background may play a role in triggering an immune response against self-antigens, current evidence suggests that immune dysregulation caused by infectious agents is the primary environmental factor responsible for initiating autoimmune diseases, as supported by both epidemiological and molecular research [29]. Prolonged immune response to infections and/or uncontrollable inflammation may lead to the emergence of autoimmune diseases and worsen the clinical course of autoimmune patients [30]. Although viral and bacterial infections have been linked to the development of autoimmune diseases, it is unlikely that exposure to these infectious agents alone will trigger an autoimmune response [31]. The onset of autoimmunity also requires the patient's genetic predisposition and/or environmental factors [32]. The production of autoantibodies is a hallmark feature of autoimmune diseases, but the pathophysiology underlying their development is still unclear [33]. Molecular mimicry with viruses and bacteria, first described over 30 years ago, has been shown to cause and/or exacerbate autoimmune diseases [34]. Viruses infect humans have the ability to mimic molecules present in the human body, which can lead to the development of autoimmunity [35]. Therefore, the dysregulated immune response to viral pathogens can disturb immune tolerance [29, 36]. Viral epitopes may be similar to human proteins, resulting in the production of cross-reactive antibodies [37]. These findings emphasize the critical role of infectious agents in the pathogenesis of autoimmune diseases and highlight the importance of considering both genetic and environmental factors in disease development. Further research is needed to fully elucidate the complex interplay between environmental and genetic factors in autoimmune diseases.

Epstein-Barr Virus (EBV), the causative agent of infectious mononucleosis, is thought to be the primary trigger for the development of many autoimmune diseases, including Multiple Sclerosis, Sjögren's Disease, and Systemic Lupus Erythematosus [38, 39]. One potential mechanism behind this link is molecular mimicry between the amino acid range 627-641 of the EBV DNA polymerase protein, which plays a role in the replication of Epstein Barr virus, exhibits molecular mimicry with the myelin basic protein amino acids between 85-99 [40]. The myelin basic protein is a protein that regulates the myelin sheath along with oligodendrocytes and Schwann cells [41]. The resulting neuro-autoimmunity, driven by the molecular mimicry between EBV DNA polymerase and myelin basic protein, leads to the development of Multiple Sclerosis [42].

Infection with the Hepatitis B virus (HBV) can cause hepatocyte destruction and inflammation, resulting in liver damage [43]. The severity of liver damage and the likelihood of liver failure vary depending on the strain of HBV involved [44]. HBV polymerase, a protein involved in viral replication, has been shown to mimic myelin proteins, which can result in neuro-autoimmune events, and this cross-reactivity may contribute to the development of neurologic complications in some HBV-infected individuals [45].

Inflammation of the myocardium, the mechanically functional part of cardiac tissue, is primarily caused by viral infections [46,47]. While many viruses can lead to myocarditis, SARS-CoV-2 is a recent addition to this list [48]. However, it is necessary to note that most viral infections responsible for myocarditis do not lead to autoimmune myocarditis [49]. Exceptions to this include Coxsackievirus and murine cytomegalovirus, which have been linked to autoimmune myocarditis [50].

β cells, responsible for the major endocrine function of the pancreas, play a critical role in regulating important metabolic processes by secreting insulin [51]. Type 1 diabetes can develop due to pancreatic cell destruction, resulting in insufficient insulin production [52]. Coxsackievirus is one of the viruses thought to be involved in the pathogenesis of type 1 diabetes [53]. The autoimmune diabetes is thought to be caused by the molecular mimicry of the P2-C protein, which is involved in Coxsackievirus replication, and the glutamate decarboxylase (GAD65) enzyme in pancreatic cells [54]. This molecular mimicry can trigger an immune response that attacks and damages cells, resulting in decreased insulin secretion [54, 55].

Systemic sclerosis is a disease in which the working system of the immune system is impaired and has systemic involvement [56]. In systemic sclerosis, there are deformities in vascular structures and abnormal fibroblast activation due to autoimmune involvement. Skin, lung, heart, musculoskeletal, renal, and gastrointestinal systems are affected by systemic sclerosis [56, 57]. Raynaud phenomenon is characteristic, especially in the fingers [56, 58]. Tetraspan novel antigen-2 (NAG-2) is a protein expressed on endothelial cells and fibroblasts [59]. Systemic sclerosis may develop due to the molecular mimicry between the UL-94 protein of the human cytomegalovirus and the NAG-2 [59, 60]. In studies with anti-UL94 antibodies, it has been proven by laboratory studies that anti-UL94 antibodies bind to NAG-2 proteins [59, 60]. It has been shown that anti-UL94 antibodies can cause systemic sclerosis by inducing endothelial cell activation and apoptosis, as well as by activating fibroblasts [59, 60].

Stiff-person syndrome is a neuroendocrine autoimmune disease in which neurons and pancreatic β cells are affected [61]. In Stiff-person syndrome, autoimmune reactions develop due to the molecular mimicry between the UL-57 protein of human cytomegalovirus and glutamate decarboxylase (GAD-65) [62]. The 674 to 687 amino acids of the UL-57 protein and the amino acids between 339 to 352 position of the GAD-65 protein constitute molecular mimicry [62]. With the targeting of GAD-65 protein by the immune system, pancreatic β cells are affected, and type-1 diabetes develops [62, 63].

In Sjögren's syndrome, an autoimmunity affecting the salivary and lacrimal glands, Coxsackie virus RNA was detected in the biopsy examinations of the salivary glands [64]. The role of molecular mimicry in the development of Sjögren's syndrome, on the other hand, has 87% sequence homology between the 31-47 amino acid sequence range of the Coxsackie virus 2B protein and the 222-229 amino acida of the Ro60 autoantigen [65]. The presence of autoantibodies against the Ro60 antigen is important in the diagnosis of Sjögren's disease [66].

Molecular Mimicry and Bacteria

As with viral infections, bacterial infections can trigger autoimmune diseases [67]. In the immune reaction against bacterial infections, lipid, protein and nucleic materials of bacteria are recognized by Toll-like receptors (TLR) expressed in various cells [68]. Toll-like receptors are classified according to their distribution in cell compartments. TLR-1, TLR-2, TLR-4, TLR-5, TLR-6 and TLR-11 are located in the endolysosomes, TLR-3, TLR-7, TLR-8 and TLR-9, bound to the plasma membrane [69]. Toll-like receptor ligands of bacteria are triacyl lipopeptide, lipoprotein, peptidoglycan, lipoteichoic acid, lipopolysaccharide, flagellin and CPG containing DNA [70]. Cytokines, chemokines, interferons and enzymes are produced through bacterial toll-like receptors, which control the immune response against bacteria [70, 71]. Cytokines, chemokines, interferons and enzymes produced due to Toll-like receptor stimulation can trigger autoimmune events by causing immune dysregulation if they are not produced regularly [72].

Streptococcal infections can also cause autoimmune reactions originating from molecular mimicry [73]. In addition, rheumatic fever, one of the most classic examples of molecular mimicry, is one of the autoimmune diseases originating from post-streptococcal molecular mimicry [74]. Some patients infected with *Streptococcus pyogenes* may develop rheumatic fever [75]. The M protein in the membrane of*Streptococcus pyogenes* bacteria is present in order to protect it from the immune system [76]. The M protein is a potent antiphagocytic protein and is the major virulence factor of group-A streptococci [76, 77]. It binds to factor H via the*Streptococcus pyogenes* M protein and inhibits C3-convertase, which is one of the most important elements of the complement system. With the inhibition of C3 convertase, the formation of C3a and C3b, which is formed by the cleavage of C3, is prevented [78]. Due to the inability to form C3b, opsonization and phagocytosis of*Streptococcus pyogenes* are inhibited. In the immune reaction against *Streptococcus pyogenes* , an immune reaction also develops against the M protein [79]. During the humoral immune response developed against the M protein, autoantibodies are formed by the deterioration of the immune tolerance of some B cells [80]. While the autoantibodies formed react against the M protein, they also self-react against the myosin protein, which is present in the cardiac tissue and undertakes the mechanical function of the cardiac cycle and causes cardiac damage [81]. Chronic rheumatoid carditis, valvular heart diseases, cardiomyopathy, heart failure, atrial arrhythmias, and pulmonary and systemic embolisms can develop as complications of cardiac damage due to rheumatic fever [82]. In addition, autoantibodies can be formed against other cardiac muscle proteins such as vimentin, collagen, and tropomyosin by the epitope spreading mechanism [80]. Another manifestation of rheumatic fever is the Sydenham chorea [83]. The formation mechanism of Sydenham chorea is also based on molecular mimicry [80]. The relationship of Sydenham chorea with molecular mimicry was understood by the cross-reaction of antibodies against N-acetyl-β-D-glucosamine found in group-A streptococci and lysoganglioside found in neurons in the central nervous system [80, 84]. In addition, some of the autoantibodies formed cause excitation by induction of Calcium calmodulin-dependent (CaM) protein kinase II [84]. Since the neurotransmitter that causes excitation is dopamine, post-synaptic Dopamine-2 (D2) receptor inhibitor haloperidol is used in the treatment of Sydenham chorea [85, 86]. The formation of musculoskeletal events due to rheumatic fever is similar to cardiac autoimmunity [80]. The mode of development of musculoskeletal events is the development of autoimmunity due to the similarity of musculoskeletal proteins and cardiac proteins [80]. The primary goal in the treatment of rheumatic fever is to reduce the burden of antigens that cause autoantibody production [87]. Therefore, it is aimed to reduce the number of bacteria carrying M protein by using penicillin [87]. In addition, most patients infected with *Streptococcus pyogenes* do not develop rheumatic fever [82]. Various risk factors are required for the development of rheumatic fever [88]. Risk factors for rheumatic fever are family history, infection with rheumatic fever streptococcal strains, and environmental factors [88].

It is caused by the molecular mimicry of Guillain-Barre syndrome (GBS) caused by *Campylobacter jejuni* infection [89]. Autoantibodies against gangliosides are produced due to infection by*Campylobacter jejuni* bacteria [89,90]. Autoantibodies (anti-ganglioside) formed against gangliosides cause destruction of gangliosides [90]. Motor neuropathies and motor nerve disorders may occur due to damage to gangliosides [91]. Following *C. jejuni*infection, Yuki et al. found that bacterial lipopolysaccharides (LPS) of*C. jejuni* resembled motor axolemma molecules (eg, GM1, GM1b and GD1a), and that sequence similarity between *C. jejuni* LPS and host ganglioside molecules resulted in pathogenic autoantibody production and GBS

development [92]. In Guillain-Barre syndrome, autoantibodies can develop against various ganglioside types such as GM1, GD1a, GT1a, GQ1b, GM1b [92,93]. In order to benefit from its anti-inflammatory effects in the treatment of Gullian barre syndrome, intravenous immunoglobulin obtained from a pool formed from healthy patients is administered [93]. Another treatment alternative is the application of plasmapheresis to remove autoantibodies from the blood [93,94].

Heat shock proteins (HSP) are involved in many physiological events [95]. One of the most important tasks of HSPs is the maturation, degradation, and re-folding of proteins [96]. In addition, HSPs are responsible for the regulation of the immune system by taking part in situations where human physiology is stressed [97]. Pseudomonas aeruginosa colonies in the lungs in cystic fibrosis, a systemic disease that affects almost all tissues [98]. Cystic fibrosis has complications affecting all systems [99]. Gastro-oesophageal reflux disease, exocrine pancreatic insufficiency, increased risk of appendicitis, meconium ileus, sinusitis, nasal polyps, persistent coughs, infertility, osteoporosis, and arthritis are complications of cystic fibrosis [99,100]. There is a correlation between anti-HSP27 autoantibodies and *P. aeruginosa* colonization in the arthritic complication of cystic fibrosis [101]. Autoimmune arthritis develops due to mimicry between pseudomonal proteins and HSP proteins [101].[101]

Lyme arthritis develops due to the molecular mimicry between*Borrelia burgdorferi* and the human proteome [102]. Lyme arthritis develops in *B. burgdorferi* caused by molecular mimicry between outer surface protein A (OspA) and human leukocyte function-associated antigen-1 (hLFA-1) [103].

COVID-19 and autoantibodies

Autoantibodies are antibodies produced by autoreactive B cells that can penetrate a wide variety of threats [104]. Autoantibodies can be produced against DNA, RNA, lipids, proteins, centromeres, chromatin and ribosomal properties [104, 105]. Loss of B cell tolerance, defective apoptosis, loss of regulatory cells and cells may cause offspring of autoantibodies [104]. Autoantibodies can be seen in IgM and IgG isotypes [104,105]. The place of autoantibodies is indispensable to recognizing and treating autoimmune clearance [106]. In organ-specific autoimmune diseases, autoantibodies are present against those with organ antigens, whereas, in systemic autoimmune diseases, no autoantibodies are present against antigens found in most tissues [104]. In autoimmune thyroiditis and Graves' disease, which are organ-specific autoimmune diseases, autoantibodies can develop against the thyroid antigens thyroglobulin, thyroperoxidase, and thyroid stimulating hormone stores [104,107]. In myesthenia gravis, another neuro-autoimmune disease, autoantibodies against the acetylcholine receptor can be formed by B cells [107]. [107] In systemic autoimmune diseases, it consists of autoantibodies against common antigens found in most tissues [108]. For example, in systemic lupus erythematosus, anti-nuclear antibodies against nuclear material consist of anti-dsDNA against DNA and anti-histone autoantibodies against histone proteins [109]. However, auto-antibodies detected in some departments controls may not spread with autoimmune diseases [110]. Viral infections can also cause autoimmune diseases in various ways [111]. Viral infections can cause autoimmune disease by mimicry, bystander activation, by adjuvant rearrangements, and by epitope spreading [112].

Autoantibodies were detected in the COVID-19 and post-COVID-19 patients [103]. It has been shown that patients with positive autoantibodies have a more severe course of COVID-19 than other cases [113]. As a result of the study of Pascolini et al. on 33 COVID-19 patients, antinuclear antibodies, anti-cytoplasmic neutrophil antibodies (ANCA), and anti-antiphospholipid antibodies (APL) showed that these autoantibodies develop due to COVID-19 [114]. Severe and critical COVID-19 patients have a higher frequency of APL autoantibody and the presence of APL antibody positivity is associated with extremely high-level ferritin, CRP, IL-6, and pulmonary thromboembolism [115]. This explains the hypercoagulable state in severe and critical COVID-19 cases and indicates that SARS-CoV-2 can induce autoimmune responses [114,116]. COVID-19 patients have a higher risk of lupus anticoagulant positivity [117]. Lupus anticoagulant-positive patients have a higher risk of thrombosis [118]. Several case reports demonstrated autoantibodies against RBC antigens which they can contribute to hemolytic anemia and are related to the severity of anemia in COVID-19 [119,120]. Some COVID-19 patients have neurologic symptoms. These patient's case reports have been shown to develop autoantibodies against contactin-associated protein 2 (anti-Caspr2), ganglioside

GD1b (anti-GD1b), and myelin oligodendrocyte glycoprotein (anti-MOG) [121,122]. COVID-19 patients can develop the hematologic system autoimmunity [123].

Material-Method

Data Collection

Structural proteins of SARS-CoV-2 (Spike, Nucleocapsid, Membrane, Envelope) were obtained from the NCBI database. The structural proteins aminoacid sequences of SARS-CoV-2 were fragmented into 8 amino acid-long peptide fragments.

Peptide Matching

The peptide-match server is an online tool to reveal the amino acid sequence similarity between amino acid sequences and desired organism [124]. Fragmented eight amino acid length peptides uploaded peptide-match server. This server predicts similarity between 8mers and human sequences [124].

Antigenicity prediction

In order to generate immune responses based on molecular mimicry, the 8mers that we constructed from SARS-CoV-2 structural proteins must be antigenic [125]. Predicted similar epitopes assessed for antigenicity in Vaxijen v2.0 antigenicity prediction server [125].

Prediction of binding affinity of peptides to TAP

The compatibility of 8mers with the TAP protein must be met for them to be presented as epitopes. Similar epitopes were analyzed for TAP affinity. For the analysis, we use the TAPreg tool [126].

Allergenicity prediction

To elicit an autoimmune response through molecular mimicry, 8mers must not possess allergenicity as this would result in the activation of an IgE-mediated response.The predicted similar epitopes were analyzed for allergenicity. For analyses of allergenicity, we use the AllerTOP v2.0 tool [127].

Toxicity prediction

Similar epitopes were analyzed for toxicity, the toxicity prediction we use the ToxinPred tool [128].

IL-10, and IFN-gamma inducing prediction

Similar epitopes were analyzed for IL-10, and IFN-gamma induction. The prediction of IL-10 [129] inducing predicted in IL-10pred, and prediction of IFN-gamma inducing predicted in IFNepitope[130] server.

HLA docking calculation

Matched best peptide (identical, antigenic, non-allergenic, non-toxic, IL-4 inducer, and IFN-gamma inducer, non-IL-10 inducer, and high affinity to TAP) docked to Class-I and Class-II MHC molecules. Class-I HLA docking simulated in CABS-dock server [131]. Structures of HLA-I molecules were retrieved from the RCSB-PDB server (4NQV, 4UQ3, 3RL2, 1X7Q, 5HGA, 5EO1, 3SPV, 1OGT, 3LKN, 1E27, 5INC). The docked models were analyzed for ΔG (kcal mol-1) and Kd (M) at 37.0 °C values. For this analysis, the PRODIGY server was used [132,133]. The Epidock server was used for DEDDSEPV peptide docking to the MHC-II receptor.

Results

Peptide Matching

Fragmented peptides imported to the peptide match server. We found six identical amino acid sequences (VNSVLLFL, VFLLVTLA, KKDKKKKA, SRSSSRSR, RRARSVAS, DEDDSEPV) to the human proteome. Table-1 shows the UniProt codes and protein names of similar proteins with identical amino acid sequences.

Table-1

List of the identified 8mers of SARS-CoV-2 that have mimicry with human proteome.

Amino acid sequence	UniProt ID	Protein Name
VNSVLLFL	O60518	Ran-binding protein 6
VFLLVTLA	Q6P4F1	Alpha-(1,3)-fucosyltransferase 10
KKDKKKKA	Q7RTP6	[F-actin]-monooxygenase MICAL3
SRSSSRSR	Q8N2M8	CLK4-associating serine/arginine-rich protein
	Q96HJ9	Protein FMC1 homolog
	Q96S94	Cyclin-L2
	Q9Y383	Putative RNA-binding protein Luc7-like 2
RRARSVAS	P37088	Amiloride-sensitive sodium channel subunit alpha
DEDDSEPV	Q9Y6X6	myosin-XVI

Antigenicity

Identical sequences must be antigenic because non-antigenic sequences cannot induce cross reactivity. Table-2 shows antigenicity and calculated antigenicity scores of identical peptides.

Table-2

Results of the predicted antigenicity scores and the antigenicity evaluation for the 8mer sequences posessing molecular mimicry.

Amino acid sequence	Antigenicity Score	Antigenicity
VNSVLLFL	0.1356	Probable NON-ANTIGEN
VFLLVTLA	0.8407	ANTIGEN
KKDKKKKA	-0.5109	Probable NON-ANTIGEN
SRSSSRSR	1.1071	ANTIGEN
RRARSVAS	0.8045	ANTIGEN
DEDDSEPV	0.6515	ANTIGEN

Prediction of binding affinity of peptides to TAP

Peptides must be transported to the endoplasmic reticulum before they can be presented to CD4+ cells by MHC-I. TAP protein carries out the transport process, so the TAP affinities of the eight amino acid length peptides were evaluated and shown in Table-3.

Allergenicity prediction

The identical peptides allergenicity predicted in AllerTOP v2.0 bioinformatic tool and shown in Table-3. Identical epitopes causing autoimmunity should not necessarily be allergic.

Toxicity prediction

The identical peptides must be non-toxic to the human body. For prediction of toxicity, the ToxinPred tool used for toxicity prediction results is shown in Table-3.

Table-3

Evaluation of the transport efficiency through to TAP protein complex involved in antigen presentation, allergenicity, and toxicity of 8mer sequences posessing molecular mimicry.

Amino acid sequence	TAP AFFINITY IC50 (nM)	Allergenicity	Toxicity
VNSVLLFL	8432.63	Non-allergen	Non-Toxin
VFLLVTLA	9921.22	Non-allergen	Non-Toxin
KKDKKKKA	22820.40	Non-allergen	Non-Toxin
SRSSSRSR	2944.01	Allergen	Non-Toxin
RRARSVAS	13850.83	Non-allergen	Non-Toxin
DEDDSEPV	55920.29	Non-allergen	Non-Toxin

IL-10, and IFN-gamma inducing peptides prediction

IFN-gamma cytokine levels increased and IL-10 levels decreased in autoimmunity. Table-4 shows IFN-gamma and IL-10 induction prediction.

Table-4

Prediction of interferon-gamma and IL-10 production induction capability of 8mer fragments of SARS-CoV-2 proteins featuring molecular mimicry between and the human proteome.

Amino acid sequence	IFN-gamma prediction	IL-10 prediction
VNSVLLFL	IFN-gamma inducer	Non-IL-10 inducer
VFLLVTLA	Non-IFN-gamma inducer	Non-IL-10 inducer
KKDKKKKA	Non-IFN-gamma inducer	Non-IL-10 inducer
SRSSSRSR	IFN-gamma inducer	Non-IL-10 inducer
RRARSVAS	Non-IFN-gamma inducer	Non-IL-10 inducer
DEDDSEPV	IFN-gamma inducer	Non-IL-10 inducer

HLA docking results

Matched best peptide (identical, antigenic, non-allergenic, non-toxic, IL-4 inducer, and IFN-gamma inducer, non-IL-10 inducer, and high affinity to TAP) docked for affinity to Class-I and Class-II MHC molecules. The MHC-I docking results show DEDDSEPV sequence has a high affinity to HLA-A*0101, HLA-A*0201, HLA-A*2402, HLA-B*0702, HLA-B*2705, HLA-B*5101, and HLA-B*5801. Table-5 shows Gibbs free energy calculation and K_d values of docking results. Figure-1 shows docked models of DEDDSEPV and HLA subtypes.

Table-5

Results of the calculation of ΔG and Kd values of DEDDSEPV sequence affinities to common HLA subtypes.

HLA subtypes	ΔG calculation	K_d (M) at 37.0
HLA-A*0101	-9.6	$1.6*10^{-7}$
HLA-A*0201	-9.4	$2.2*10^{-7}$
HLA-A*0301	-8.3	$1.3*10^{-6}$
HLA-A*1101	-7.8	$3.3*10^{-6}$

HLA-A*2402	-9.3	$2.6*10^{-7}$
HLA-B*0702	-9.2	$3.4*10^{-7}$
HLA-B*0801	-7.9	$2.8*10^{-6}$
HLA-B*2705	-9.4	$2.5*10^{-7}$
HLA-B*3501	-7.9	$2.7*10^{-6}$
HLA-B*5101	-9.8	$1.2*10^{-7}$
HLA-B*5801	-10.3	$5.3*10^{-8}$

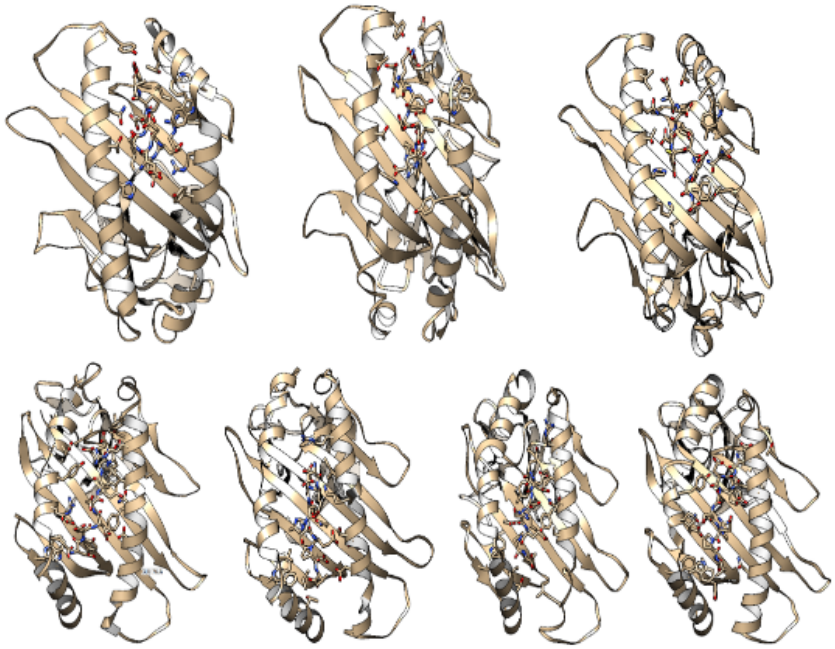

Figure-1

These models depict the docked structures of DEDDSEPV with MHC-I receptors. The top three models represent the HLA-A*0101, HLA-A*0201, and HLA-A*2402, while the bottom four models represent the HLA-B*0702, HLA-B*2705, HLA-B*5101, and HLA-B*5801 receptors, respectively.

Discussion

COVID-19 is a novel pandemic that has had significant global health consequences. The clinical course of COVID-19 is similar to systemic autoimmune diseases in some patients. Biological and chemical anti-inflammatory medications are used in the treatment of autoimmunity in severe and critical patients with COVID-19 [134,135]. In some cases, the immune response to COVID-19 resembles the immune response that develops in patients with systemic autoimmunity [136]. This situation can cause multi-organ to represent presentation in both COVID-19 and autoimmune patients [137]. The SARS-CoV-2 virus can disturb the self-tolerance of host antigens at least in part through molecular mimicry. Indeed, the development of autoantibodies and sometimes organ-specific (e.g., GBS) or systemic (e.g., SLE-like disease) autoimmunity has been observed in COVID-19. We used immunoinformatics and proteomics tools to explain the autoimmune conditions that may develop during and after COVID-19 infection and the previously unknown pathophysiology of neurological events in COVID-19. In vitro and in vivo studies have been carried out in previous studies in the literature to determine the molecular mimicry between organisms that can cause autoimmune diseases and the human proteome. With the development of machine learning and artificial

intelligence-based bioinformatics tools, molecular mimicries between organisms and the human proteome can be detected using the methodology we use. As a limitation of our study, like every algorithm, bioinformatics tools have a margin of error. Therefore, the DEDDSEPV amino acid sequence, which we determined as a potential molecular mimicry with 100% amino acid sequence similarity in our study, may need to be confirmed in vitro or in vivo. In the study of Churilov et al., using in silico techniques, spike protein and autoantigens of type-1 diabetes-related and Addison autoimmunities were defined as molecular mimicry [138]. Nunez-Castilla et al. described potential molecular mimicry using structural bioinformatics techniques in their study [139]. In their study, Nunez-Castilla et al. contributed to the elucidation of the pathophysiology of autoimmune thyroiditis due to SARS-CoV-2 infection by identifying the presence of molecular mimicry between the TQLPP amino acid sequence in the Spike protein and human thyroid peroxidase [139]. In our study, we defined the molecular mimicry between SARS-CoV-2 and the human proteome using immunoinformatic techniques. Obviously, by using both techniques together, more accurate results can be obtained and it is easy to understand the autoimmunities between which organisms and the human proteome.

Conclusion

SARS-CoV-2 eight amino acid length peptides matched the human proteome and found six identical peptides. The peptide sequence with the highest probability of cross-reactivity was selected and analyzed. Selected peptide docked MHC-I and MHC-II receptors, these docking results show DEDDSEPV sequence can cause cross-reactivity to human myosin-16. Myosin-16 is a motor protein and is highly expressed in the central nervous system. Myosin-16 protein is also highly expressed in endocrine tissues (especially the pituitary gland), liver, and gallbladder. In our study, we proved by using in-silico methods that the DEDDSEPV peptide sequence can cause cross-reactivity. Auto-antibodies that may develop against myosin-16 may explain the neurological symptoms and diseases that may develop due to COVID-19. This could explain the pathophysiologic symptoms and diseases that may develop due to COVID-19 of the endocrine system, which affects the entire physiology of the human body, such as the immune system. Liver function tests are high in critical and severe COVID-19 patients. Since myosin-16 is expressed at a high level in the liver tissue, it can explain the irregularity in liver function tests. Our study is the first in the literature to try to define the molecular mimicry between SARS-CoV-2 and the human proteome using immunoinformatic techniques. We think that in the future it will illuminate the similarity between other organisms and the human proteome using the methodology in our study. It may contribute to elucidating the pathophysiology of autoimmune diseases by elucidating the similarity between other organisms and the human proteome. When molecular mimicries are illuminated and which organism triggers which autoimmunity, removal of the triggering organism or reduction of its antigenic load can open a new era in the treatment of autoimmune diseases.

Funding

The authors declare that they did not obtain funding for this work

Declaration of Competing Interest

A.S. and H.B. are members of the management board, while F.H.K and C.B.Ş are researchers at silicosome Biotechnology (Konya, Turkey).

REFERENCES

1. V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. Nature Reviews Microbiology. 2021;19(3):155-170.
2. Wang M-Y, Zhao R, Gao L-J, Gao X-F, Wang D-P, Cao J-M. SARS-CoV-2: structure, biology, and structure-based therapeutics development. Frontiers in cellular and infection microbiology. 2020:724.
3. Soma VL, Shust GF, Ratner AJ. Multisystem inflammatory syndrome in children. Current Opinion in Pediatrics. 2021;33(1):152-158.

4. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. Physiological genomics. 2020;52(11):549-557.

5. Parasher A. COVID-19: Current understanding of its pathophysiology, clinical presentation and treatment. Postgraduate medical journal. 2021;97(1147):312-320.

6. Adil MT, Rahman R, Whitelaw D, et al. SARS-CoV-2 and the pandemic of COVID-19. Postgraduate medical journal. 2021;97(1144):110-116.

7. Arya R, Kumari S, Pandey B, et al. Structural insights into SARS-CoV-2 proteins. Journal of molecular biology. 2021;433(2):166725.

8. Scialo F, Daniele A, Amato F, et al. ACE2: the major cell entry receptor for SARS-CoV-2. Lung. 2020;198(6):867-877.

9.

10. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine. 2020;8(5):475-481.

11. Guan W-j, Ni Z-y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020;382(18):1708-1720.

12. Mulay A, Konda B, Garcia Jr G, et al. SARS-CoV-2 infection of primary human lung epithelium for COVID-19 modeling and drug discovery. Cell reports. 2021;35(5):109055.

13. Conti P, Ronconi G, Caraffa A, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. J Biol Regul Homeost Agents. 2020;34(2):327-331.

14. Habashi NM, Camporota L, Gatto LA, Nieman G. Functional pathophysiology of SARS-CoV-2-induced acute lung injury and clinical implications. Journal of applied physiology. 2021;130(3):877-891.

15. Machhi J, Herskovitz J, Senan AM, et al. The natural history, pathobiology, and clinical manifestations of SARS-CoV-2 infections. Journal of Neuroimmune Pharmacology. 2020;15(3):359-386.

16. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and multiorgan response. Current problems in cardiology. 2020;45(8):100618.

17. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA internal medicine. 2020;180(7):934-943.

18. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The lancet. 2020;395(10229):1054-1062.

19. Catanzaro M, Fagiani F, Racchi M, Corsini E, Govoni S, Lanni C. Immune response in COVID-19: addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2. Signal transduction and targeted therapy. 2020;5(1):1-10.

20. Ji P, Zhu J, Zhong Z, et al. Association of elevated inflammatory markers and severe COVID-19: A meta-analysis. Medicine. 2020;99(47)

21. Sadeghi A, Tahmasebi S, Mahmood A, et al. Th17 and Treg cells function in SARS-CoV2 patients compared with healthy controls. Journal of cellular physiology. 2021;236(4):2829-2839.

22. Parackova Z, Bloomfield M, Klocperk A, Sediva A. Neutrophils mediate Th17 promotion in COVID-19 patients. Journal of leukocyte biology. 2021;109(1):73-76.

23. Toniati P, Piva S, Cattalini M, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. Autoimmunity reviews. 2020;19(7):102568.

24. Satarker S, Tom AA, Shaji RA, Alosious A, Luvis M, Nampoothiri M. JAK-STAT pathway inhibition and their implications in COVID-19 therapy. Postgraduate medicine. 2021;133(5):489-507.

25. Liu Y, Sawalha AH, Lu Q. COVID-19 and autoimmune diseases. Current opinion in rheumatology. 2021;33(2):155.

26. Galeotti C, Bayry J. Autoimmune and inflammatory diseases following COVID-19. Nature Reviews Rheumatology. 2020;16(8):413-414.

27. Theofilopoulos AN, Kono DH, Baccala R. The multiple pathways to autoimmunity. Nature immunology. 2017;18(7):716-724.

28. Rosenblum MD, Remedios KA, Abbas AK. Mechanisms of human autoimmunity. The Journal of clinical investigation. 2015;125(6):2228-2233.

29. Getts DR, Chastain EM, Terry RL, Miller SD. Virus infection, antiviral immunity, and autoimmunity. Immunological reviews. 2013;255(1):197-209.

30. Spihlman AP, Gadi N, Wu SC, Moulton VR. COVID-19 and systemic lupus erythematosus: focus on immune response and therapeutics. Frontiers in Immunology. 2020:2861.

31. Sfriso P, Ghirardello A, Botsios C, et al. Infections and autoimmunity: the multifaceted relationship. Journal of leukocyte biology. 2010;87(3):385-395.

32. Maddur MS, Vani J, Lacroix-Desmazes S, Kaveri S, Bayry J. Autoimmunity as a predisposition for infectious diseases. PLoS pathogens. 2010;6(11):e1001077.

33. Conigliaro P, Triggianese P, Ballanti E, Perricone C, Perricone R, Chimenti MS. Complement, infection, and autoimmunity. Current Opinion in Rheumatology. 2019;31(5):532-541.

34. Rojas M, Restrepo-Jiménez P, Monsalve DM, et al. Molecular mimicry and autoimmunity. Journal of autoimmunity. 2018;95:100-123.

35. Fujinami RS, Matthias G. von Herrath, Urs Christen, and J. Lindsay Whitton. 2006."Molecular Mimicry, Bystander Activation, or Viral Persistence: Infections and Autoimmune Disease.". Clinical Microbiology Reviews. 19(1):80-94.

36. Lazarevic I, Pravica V, Miljanovic D, Cupic M. Immune evasion of SARS-CoV-2 emerging variants: what have we learnt so far? Viruses. 2021;13(7):1192.

37. Venigalla SSK, Premakumar S, Janakiraman V. A possible role for autoimmunity through molecular mimicry in alphavirus mediated arthritis. Scientific reports. 2020;10(1):1-12.

38. Houen G, Trier NH. Epstein-Barr Virus and Systemic Autoimmune Diseases. Front Immunol. 2021;11:587380. Published 2021 Jan 7. doi:10.3389/fimmu.2020.587380

39. Pender MP, Csurhes PA, Lenarczyk A, Pfluger CM, Burrows SR. Decreased T cell reactivity to Epstein-Barr virus infected lymphoblastoid cell lines in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2009;80(5):498-505. doi:10.1136/jnnp.2008.161018

40. Lang HL, Jacobsen H, Ikemizu S, et al. A functional and structural basis for TCR cross-reactivity in multiple sclerosis. Nat Immunol. 2002;3(10):940-943. doi:10.1038/ni835

41. Boggs JM. Myelin basic protein: a multifunctional protein. Cell Mol Life Sci. 2006;63(17):1945-1961. doi:10.1007/s00018-006-6094-7

42. Holmøy T, Kvale EØ, Vartdal F. Cerebrospinal fluid CD4+ T cells from a multiple sclerosis patient cross-recognize Epstein-Barr virus and myelin basic protein. J Neurovirol. 2004;10(5):278-283. doi:10.1080/13550280490499524

43. Chisari FV, Isogawa M, Wieland SF. Pathogenesis of hepatitis B virus infection. Pathol Biol (Paris). 2010;58(4):258-266. doi:10.1016/j.patbio.2009.11.001

44. Suhail M, Abdel-Hafiz H, Ali A, et al. Potential mechanisms of hepatitis B virus induced liver injury. World J Gastroenterol. 2014;20(35):12462-12472. doi:10.3748/wjg.v20.i35.12462

45. Fujinami RS, Oldstone MB. Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. Science. 1985;230(4729):1043-1045. doi:10.1126/science.2414848

46.

47. L. Andr´eoletti, et al., Active Coxsackieviral B infection is associated with disruption of dystrophin in endomyocardial tissue of patients who died suddenly of acute myocardial infarction, J. Am. Coll. Cardiol. 50 (2007) 2207–2214, https://doi.org/10.1016/j.jacc.2007.07.080.

48. D. Gamba, G. Dolivo, C. Bozic, [Cases of viral myocarditis in newborn infants], Rev. Med. Suisse Romande 86 (1966) 206–215.

49. U. Kühl, et al., Viral persistence in the myocardium is associated with progressive cardiac dysfunction, Circulation 112 (2005) 1965–1970, https://doi.org/ 10.1161/CIRCULATIONAHA.105.548156.

50. P. Krebs, et al., Molecular mapping of autoimmune B cell responses in experimental myocarditis, J. Autoimmun. 28 (2007) 224–233, https://doi.org/ 10.1016/j.jaut.2007.01.003.

51.

52. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. Lancet. 2018;391(10138):2449-2462. doi:10.1016/S0140-6736(18)31320-5

53. Green J, Casabonne D, Newton R. Coxsackie B virus serology and Type 1 diabetes mellitus: a systematic review of published case-control studies. Diabet Med. 2004;21(6):507-514. doi:10.1111/j.1464-5491.2004.01182.x

54. Tian J, Lehmann PV, Kaufman DL. T cell cross-reactivity between coxsackievirus and glutamate decarboxylase is associated with a murine diabetes susceptibility allele. J Exp Med 1994;180:1979-84.

55. Solimena M, Folli F, Aparisi R, Pozza G, De Camilli P. Autoantibodies to GABA-ergic neurons and pancreatic beta cells in stiff-man syndrome. N Engl J Med. 1990;322(22):1555-1560. doi:10.1056/NEJM199005313222202

56. Allanore Y, Simms R, Distler O, et al. Systemic sclerosis. Nat Rev Dis Primers. 2015;1:15002. Published 2015 Apr 23. doi:10.1038/nrdp.2015.2

57. Sobolewski P, Maślińska M, Wieczorek M, et al. Systemic sclerosis - multidisciplinary disease: clinical features and treatment. Reumatologia. 2019;57(4):221-233. doi:10.5114/reum.2019.87619

58. Hughes M, Allanore Y, Chung L, Pauling JD, Denton CP, Matucci-Cerinic M. Raynaud phenomenon and digital ulcers in systemic sclerosis [published correction appears in Nat Rev Rheumatol. 2021 Apr;17(4):246]. Nat Rev Rheumatol. 2020;16(4):208-221. doi:10.1038/s41584-020-0386-4

59. Lunardi C, Bason C, Navone R, et al. Systemic sclerosis immunoglobulin G autoantibodies bind the human cytomegalovirus late protein UL94 and induce apoptosis in human endothelial cells. Nat Med. 2000;6(10):1183-1186. doi:10.1038/80533

60. Lunardi C, Dolcino M, Peterlana D, et al. Antibodies against human cytomegalovirus in the pathogenesis of systemic sclerosis: a gene array approach. PLoS Med. 2006;3(1):e2. doi:10.1371/journal.pmed.0030002

61. Hadavi S, Noyce AJ, Leslie RD, Giovannoni G. Stiff person syndrome. Pract Neurol. 2011;11(5):272-282. doi:10.1136/practneurol-2011-000071

62. Hiemstra HS, Schloot NC, van Veelen PA, et al. Cytomegalovirus in autoimmunity: T cell crossreactivity to viral antigen and autoantigen glutamic acid decarboxylase. Proc Natl Acad Sci U S A. 2001;98(7):3988-3991. doi:10.1073/pnas.071050898

63. Ali F, Rowley M, Jayakrishnan B, Teuber S, Gershwin ME, Mackay IR. Stiff-person syndrome (SPS) and anti-GAD-related CNS degenerations: protean additions to the autoimmune central neuropathies. J Autoimmun. 2011;37(2):79-87. doi:10.1016/j.jaut.2011.05.005

64. Triantafyllopoulou A, Tapinos N, Moutsopoulos HM. Evidence for coxsackievirus infection in primary Sjögren's syndrome. Arthritis Rheum. 2004;50(9):2897-2902. doi:10.1002/art.20463

65. Stathopoulou EA, Routsias JG, Stea EA, Moutsopoulos HM, Tzioufas AG. Cross-reaction between antibodies to the major epitope of Ro60 kD autoantigen and a homologous peptide of Coxsackie virus 2B protein. Clin Exp Immunol. 2005;141(1):148-154. doi:10.1111/j.1365-2249.2005.02812.x

66. Ching KH, Burbelo PD, Gonzalez-Begne M, et al. Salivary anti-Ro60 and anti-Ro52 antibody profiles to diagnose Sjogren's Syndrome. J Dent Res. 2011;90(4):445-449. doi:10.1177/0022034510390811

67. Qiu CC, Caricchio R, Gallucci S. Triggers of Autoimmunity: The Role of Bacterial Infections in the Extracellular Exposure of Lupus Nuclear Autoantigens. Front Immunol. 2019;10:2608. Published 2019 Nov 8. doi:10.3389/fimmu.2019.02608

68. Gerold G, Zychlinsky A, de Diego JL. What is the role of Toll-like receptors in bacterial infections?. Semin Immunol. 2007;19(1):41-47. doi:10.1016/j.smim.2006.12.003

69. Goulopoulou S, McCarthy CG, Webb RC. Toll-like Receptors in the Vascular System: Sensing the Dangers Within. Pharmacol Rev. 2016;68(1):142-167. doi:10.1124/pr.114.010090

70. Patel RM, Lin PW. Developmental biology of gut-probiotic interaction. Gut Microbes. 2010;1(3):186-195. doi:10.4161/gmic.1.3.12484

71. Duan T, Du Y, Xing C, Wang HY, Wang RF. Toll-Like Receptor Signaling and Its Role in Cell-Mediated Immunity. Front Immunol. 2022;13:812774. Published 2022 Mar 3. doi:10.3389/fimmu.2022.812774

72. Moreth K, Brodbeck R, Babelova A, et al. The proteoglycan biglycan regulates expression of the B cell chemoattractant CXCL13 and aggravates murine lupus nephritis. J Clin Invest. 2010;120(12):4251-4272. doi:10.1172/JCI42213

73. Cunningham MW. Molecular Mimicry, Autoimmunity, and Infection: The Cross-Reactive Antigens of Group A Streptococci and their Sequelae. Microbiol Spectr. 2019;7(4):10.1128/microbiolspec.GPP3-0045-2018. doi:10.1128/microbiolspec.GPP3-0045-2018

74. Guilherme L, Kalil J, Cunningham M. Molecular mimicry in the autoimmune pathogenesis of rheumatic heart disease. Autoimmunity. 2006;39(1):31-39. doi:10.1080/08916930500484674

75. Dinkla K, Rohde M, Jansen WT, Kaplan EL, Chhatwal GS, Talay SR. Rheumatic fever-associated Streptococcus pyogenes isolates aggregate collagen. J Clin Invest. 2003;111(12):1905-1912. doi:10.1172/JCI17247

76. Carlsson F, Berggård K, Stålhammar-Carlemalm M, Lindahl G. Evasion of phagocytosis through cooperation between two ligand-binding regions in Streptococcus pyogenes M protein. J Exp Med.

2003;198(7):1057-1068. doi:10.1084/jem.20030543

77. Metzgar D, Zampolli A. The M protein of group A Streptococcus is a key virulence factor and a clinically relevant strain identification marker. Virulence. 2011;2(5):402-412. doi:10.4161/viru.2.5.16342

78. Agrahari G, Liang Z, Glinton K, Lee SW, Ploplis VA, Castellino FJ. Streptococcus pyogenes Employs Strain-dependent Mechanisms of C3b Inactivation to Inhibit Phagocytosis and Killing of Bacteria. J Biol Chem. 2016;291(17):9181-9189. doi:10.1074/jbc.M115.704221

79. Courtney HS, Hasty DL, Dale JB. Anti-phagocytic mechanisms of Streptococcus pyogenes: binding of fibrinogen to M-related protein. Mol Microbiol. 2006;59(3):936-947. doi:10.1111/j.1365-2958.2005.04977.x

80. Cunningham MW. Streptococcus and rheumatic fever. Curr Opin Rheumatol. 2012;24(4):408-416. doi:10.1097/BOR.0b013e32835461d3

81. Quinn A, Kosanke S, Fischetti VA, Factor SM, Cunningham MW. Induction of autoimmune valvular heart disease by recombinant streptococcal m protein. Infect Immun. 2001;69(6):4072-4078. doi:10.1128/IAI.69.6.4072-4078.2001

82. Carapetis JR, Beaton A, Cunningham MW, et al. Acute rheumatic fever and rheumatic heart disease. Nat Rev Dis Primers. 2016;2:15084. Published 2016 Jan 14. doi:10.1038/nrdp.2015.84

83. Dean SL, Singer HS. Treatment of Sydenham's Chorea: A Review of the Current Evidence. Tremor Other Hyperkinet Mov (N Y). 2017;7:456. Published 2017 Jun 1. doi:10.7916/D8W95GJ2

84. Kirvan CA, Swedo SE, Kurahara D, Cunningham MW. Streptococcal mimicry and antibody-mediated cell signaling in the pathogenesis of Sydenham's chorea. Autoimmunity. 2006;39(1):21-29. doi:10.1080/08916930500484757

85. Walker KG, Wilmshurst JM. An update on the treatment of Sydenham's chorea: the evidence for established and evolving interventions. Ther Adv Neurol Disord. 2010;3(5):301-309. doi:10.1177/1756285610382063

86. Froemming JS, Lam YW, Jann MW, Davis CM. Pharmacokinetics of haloperidol. Clin Pharmacokinet. 1989;17(6):396-423. doi:10.2165/00003088-198917060-00004

87. Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation. 2009;119(11):1541-1551. doi:10.1161/CIRCULATIONAHA.109.191959

88. Baker MG, Gurney J, Oliver J, et al. Risk Factors for Acute Rheumatic Fever: Literature Review and Protocol for a Case-Control Study in New Zealand. Int J Environ Res Public Health. 2019;16(22):4515. Published 2019 Nov 15. doi:10.3390/ijerph16224515

89. Yuki N. Infectious origins of, and molecular mimicry in, Guillain-Barré and Fisher syndromes. Lancet Infect Dis. 2001;1(1):29-37. doi:10.1016/S1473-3099(01)00019-6

90. Yu RK, Usuki S, Ariga T. Ganglioside molecular mimicry and its pathological roles in Guillain-Barré syndrome and related diseases. Infect Immun. 2006;74(12):6517-6527. doi:10.1128/IAI.00967-06

91. Yuki N. Guillain-Barré syndrome and anti-ganglioside antibodies: a clinician-scientist's journey. Proc Jpn Acad Ser B Phys Biol Sci. 2012;88(7):299-326. doi:10.2183/pjab.88.299

92. Yuki N, Hartung HP. Guillain-Barré syndrome [published correction appears in N Engl J Med. 2012 Oct 25;367(17):1673]. N Engl J Med. 2012;366(24):2294-2304. doi:10.1056/NEJMra1114525

93. van den Berg B, Walgaard C, Drenthen J, Fokke C, Jacobs BC, van Doorn PA. Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis. Nat Rev Neurol. 2014;10(8):469-482. doi:10.1038/nrneurol.2014.121

94. Raphaël JC, Chevret S, Hughes RA, Annane D. Plasma exchange for Guillain-Barré syndrome. Cochrane Database Syst Rev. 2002;(2):CD001798. doi:10.1002/14651858.CD001798

95. Park CJ, Seo YS. Heat Shock Proteins: A Review of the Molecular Chaperones for Plant Immunity. Plant Pathol J. 2015;31(4):323-333. doi:10.5423/PPJ.RW.08.2015.0150

96. Whitley D, Goldberg SP, Jordan WD. Heat shock proteins: a review of the molecular chaperones. J Vasc Surg. 1999;29(4):748-751. doi:10.1016/s0741-5214(99)70329-0

97. Zügel U, Kaufmann SH. Role of heat shock proteins in protection from and pathogenesis of infectious diseases. Clin Microbiol Rev. 1999;12(1):19-39. doi:10.1128/CMR.12.1.19

98. Sousa AM, Pereira MO. Pseudomonas aeruginosa Diversification during Infection Development in Cystic Fibrosis Lungs-A Review. Pathogens. 2014;3(3):680-703. Published 2014 Aug 18. doi:10.3390/pathogens3030680

99. Naehrig S, Chao CM, Naehrlich L. Cystic Fibrosis. Dtsch Arztebl Int. 2017;114(33-34):564-574. doi:10.3238/arztebl.2017.0564

100. Tewkesbury DH, Robey RC, Barry PJ. Progress in precision medicine in cystic fibrosis: a focus on CFTR modulator therapy. Breathe (Sheff). 2021;17(4):210112. doi:10.1183/20734735.0112-2021

101. al-Shamma MR, McSharry C, McLeod K, McCruden EA, Stack BH. Role of heat shock proteins in the pathogenesis of cystic fibrosis arthritis. Thorax. 1997;52(12):1056-1059. doi:10.1136/thx.52.12.1056

102. Raveche ES, Schutzer SE, Fernandes H, et al. Evidence of Borrelia autoimmunity-induced component of Lyme carditis and arthritis. J Clin Microbiol. 2005;43(2):850-856. doi:10.1128/JCM.43.2.850-856.2005

103. Gross DM, Forsthuber T, Tary-Lehmann M, et al. Identification of LFA-1 as a candidate autoantigen in treatment-resistant Lyme arthritis. Science. 1998;281(5377):703-706. doi:10.1126/science.281.5377.703

104. Elkon K, Casali P. Nature and functions of autoantibodies. Nat Clin Pract Rheumatol. 2008;4(9):491-498. doi:10.1038/ncprheum0895

105. Silverman GJ, Srikrishnan R, Germar K, et al. Genetic imprinting of autoantibody repertoires in systemic lupus erythematosus patients. Clin Exp Immunol. 2008;153(1):102-116. doi:10.1111/j.1365-2249.2008.03680.x

106. Ludwig RJ, Vanhoorelbeke K, Leypoldt F, et al. Mechanisms of Autoantibody-Induced Pathology. Front Immunol. 2017;8:603. Published 2017 May 31. doi:10.3389/fimmu.2017.00603

107. Lopomo A, Berrih-Aknin S. Autoimmune Thyroiditis and Myasthenia Gravis. Front Endocrinol (Lausanne). 2017;8:169. Published 2017 Jul 13. doi:10.3389/fendo.2017.00169

108. Shi G, Zhang J, Zhang Z, Zhang X. Systemic Autoimmune Diseases. Clin Dev Immunol. 2013;2013:728574. doi:10.1155/2013/728574

109. Pisetsky DS, Lipsky PE. New insights into the role of antinuclear antibodies in systemic lupus erythematosus. Nat Rev Rheumatol. 2020;16(10):565-579. doi:10.1038/s41584-020-0480-7

110. Lernmark A. Autoimmune diseases: are markers ready for prediction?. J Clin Invest. 2001;108(8):1091-1096. doi:10.1172/JCI14234

111. Smatti MK, Cyprian FS, Nasrallah GK, Al Thani AA, Almishal RO, Yassine HM. Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms. Viruses. 2019;11(8):762. Published 2019 Aug 19. doi:10.3390/v11080762

112. Johnson D, Jiang W. Infectious diseases, autoantibodies, and autoimmunity [published online ahead of print, 2022 Dec 2]. J Autoimmun. 2022;102962. doi:10.1016/j.jaut.2022.102962

113. Chang SE, Feng A, Meng W, et al. New-onset IgG autoantibodies in hospitalized patients with COVID-19. Nature communications. 2021;12(1):1-15.

114. Pascolini S, Vannini A, Deleonardi G, et al. COVID-19 and immunological dysregulation: can autoantibodies be useful? Clinical and Translational Science. 2021;14(2):502-508.

115. Ehrenfeld M, Tincani A, Andreoli L, et al. Covid-19 and autoimmunity. Autoimmunity reviews. 2020;19(8):102597.

116. Gil MR, Barouqa M, Szymanski J, Gonzalez-Lugo JD, Rahman S, Billett HH. Assessment of lupus anticoagulant positivity in patients with coronavirus disease 2019 (COVID-19). JAMA network open. 2020;3(8):e2017539-e2017539.

117. Gooding R, Myers B, Salta S. Lupus Anticoagulant in Patients with Covid-19. N Engl J Med. 2020:1893-1893.

118. Harzallah I, Debliquis A, Drenou B. Lupus anticoagulant is frequent in patients with Covid-19: Response to Reply. Journal of Thrombosis and Haemostasis. 2020;

119. Jensen CE, Wilson S, Thombare A, Weiss S, Ma A. Cold agglutinin syndrome as a complication of Covid-19 in two cases. Clinical Infection in Practice. 2020;7:100041.

120. Berzuini A, Bianco C, Paccapelo C, et al. Red cell–bound antibodies and transfusion requirements in hospitalized patients with COVID-19. Blood. 2020;136(6):766-768.

121. Pinto AA, Carroll LS, Nar V, Varatharaj A, Galea I. CNS inflammatory vasculopathy with antimyelin oligodendrocyte glycoprotein antibodies in COVID-19. Neurology-Neuroimmunology Neuroinflammation. 2020;7(5)

122. Guilmot A, Maldonado Slootjes S, Sellimi A, et al. Immune-mediated neurological syndromes in SARS-CoV-2-infected patients. Journal of neurology. 2021;268(3):751-757.

123. Taherifard E, Taherifard E, Movahed H, Mousavi MR. Hematologic autoimmune disorders in the course of COVID-19: a systematic review of reported cases. Hematology. 2021;26(1):225-239.

124. Chen C, Li Z, Huang H, Suzek BE, Wu CH, Consortium U. A fast peptide match service for UniProt knowledgebase. Bioinformatics. 2013;29(21):2808-2809.

125. Doytchinova IA, Flower DR. VaxiJen: a server for prediction of protective antigens, tumour antigens and subunit vaccines. BMC bioinformatics. 2007;8(1):1-7.

126. Diez-Rivero CM, Chenlo B, Zuluaga P, Reche PA. Quantitative modeling of peptide binding to TAP using support vector machine. Proteins: Structure, Function, and Bioinformatics. 2010;78(1):63-72.

127. Dimitrov I, Bangov I, Flower DR, Doytchinova I. AllerTOP v. 2—a server for in silico prediction of allergens. Journal of molecular modeling. 2014;20(6):1-6.

128. Gupta S, Kapoor P, Chaudhary K, et al. In silico approach for predicting toxicity of peptides and proteins. PloS one. 2013;8(9):e73957.

129. Nagpal G, Usmani SS, Dhanda SK, et al. Computer-aided designing of immunosuppressive peptides based on IL-10 inducing potential. Scientific reports. 2017;7(1):1-10.

130. Dhanda SK, Vir P, Raghava GP. Designing of interferon-gamma inducing MHC class-II binders. Biology direct. 2013;8(1):1-15.

131. Blaszczyk M, Ciemny MP, Kolinski A, Kurcinski M, Kmiecik S. Protein–peptide docking using CABSdock and contact information. Briefings in bioinformatics. 2019;20(6):2299-2305.

132. Vangone A, Bonvin AM. Contacts-based prediction of binding affinity in protein–protein complexes. elife. 2015;4:e07454.

133. Xue LC, Rodrigues JP, Kastritis PL, Bonvin AM, Vangone A. PRODIGY: a web server for predicting the binding affinity of protein–protein complexes. Bioinformatics. 2016;32(23):3676-3678.

134. Kaminski MA, Sunny S, Balabayova K, et al. Tocilizumab therapy for COVID-19: A comparison of subcutaneous and intravenous therapies. International Journal of Infectious Diseases. 2020;101:59-64.

135. Iglesias-Julian E, Lopez-Veloso M, de-la-Torre-Ferrera N, et al. High dose subcutaneous Anakinra to treat acute respiratory distress syndrome secondary to cytokine storm syndrome among severely ill COVID-19 patients. Journal of autoimmunity. 2020;115:102537.

136. Mortaz E, Tabarsi P, Varahram M, Folkerts G, Adcock IM. The immune response and immunopathology of COVID-19. Frontiers in immunology. 2020:2037.

137. Ramos-Casals M, Brito-Zeron P, Mariette X. Systemic and organ-specific immune-related manifestations of COVID-19. Nature Reviews Rheumatology. 2021;17(6):315-332.

138. Churilov LP, Normatov MG, Utekhin VJ. Molecular Mimicry between SARS-CoV-2 and Human Endocrinocytes: A Prerequisite of Post-COVID-19 Endocrine Autoimmunity?. Pathophysiology. 2022;29(3):486-494. Published 2022 Aug 25. doi:10.3390/pathophysiology29030039

139. Nunez-Castilla J, Stebliankin V, Baral P, et al. Potential Autoimmunity Resulting from Molecular Mimicry between SARS-CoV-2 Spike and Human Proteins. Viruses. 2022;14(7):1415. Published 2022 Jun 28. doi:10.3390/v14071415

Hosted file

`Figures.docx` available at https://authorea.com/users/620204/articles/644362-myosin-16-mimicries-may-explain-post-covid-19-related-neurological-consequences

Hosted file

`Tables.docx` available at https://authorea.com/users/620204/articles/644362-myosin-16-mimicries-may-explain-post-covid-19-related-neurological-consequences