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Molecular Mimicry Analyses Unveiled the Human Herpes Simplex and Poxvirus Epitopes as Possible Candidates to Incite Autoimmunity

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Abstract: Clinical epidemiological studies have reported that viral infections cause autoimmune pathology in humans. Host-pathogen protein sequences and structure-based molecular mimicry cause autoreactive T cells to cross-activate. The aim of the current study was to implement immunoinformatics approaches to infer sequence- and structure-based molecular mimicry between viral and human proteomic datasets. The protein sequences of all the so far known human-infecting viruses were obtained from the VIPR database, and complete human proteome data were retrieved from the NCBI repository. Based on a predefined, stringent threshold of comparative sequence analyses, 24 viral proteins were identified with significant sequence similarity to human proteins. PathDIP identified the enrichment of these homologous proteins in nine metabolic pathways with a p -value < 0.0001 . Several viral and human mimic epitopes from these homologous proteins were predicted as strong binders of human HLA alleles, with $IC_{50} < 50$ nM. Downstream molecular docking analyses identified that lead virus-human homologous epitopes feasibly interact with HLA and TLR4 types of immune receptors. The vast majority of these top-hit homolog epitopic peptides belong to the herpes simplex and poxvirus families. These lead epitope biological sequences and 3D structural-based molecular mimicry may be promising for interpreting herpes simplex virus and poxvirus infection-mediated autoimmune disorders in humans.

Keywords: molecular mimicry; autoimmune disorders; cross-reactive epitopes; viral infection; sequence and structural homology

1. Introduction

The human immune system defends against various diseases by recognizing and eliminating pathogens and damaged cells. If this approach is unsuccessful, an elicited immune response is initiated against the body's healthy cells and tissues, resulting in various autoimmune illnesses (AIDs) [1,2]. Over 100 million individuals worldwide are infected with over 80 distinct types of deadly AIDs [1,3–5]. AIDs are caused by a combination of factors, including age, genetics, environment, and microbial infections [6]. Understanding the underlying molecular mechanisms responsible for autoreactive T cells and the pathophysiology of AIDs is critical. The human immune system maintains a delicate equilibrium to distinguish between self- and non-self-antigens. Most autoreactive T cells are normally destroyed. However, only a small fraction survive, and are assumed to be the cause of autoimmune diseases. Although the human immune system has well-established

mechanisms for removing or tolerating the autoreactive T and B cells, nonetheless, these cells are commonly activated and cause devastating AIDs [7–9]. The T-cell-specific autoimmune illnesses identified in the literature include multiple sclerosis (MS), human type-1 diabetes, type-2 autoimmune hepatitis, meningitis, primary biliary cirrhosis, and autoimmune arthritis [2,10,11]. However, the molecular mechanisms underlying these diseases remain unclear.

One of the key mechanisms that causes autoimmune disorders is molecular mimicry, in which the pathogenic antigens exhibit sequence and structural resemblance to host self-antigens. Viruses are hypothesized to contain antigens that are structurally similar to self-antigens and activate B and T cells, resulting in a cross-reactive response against both self- and non-self antigens, which leads to autoimmunity [12–14]. Several viral species have been associated with AIDs. For instance, the herpes simplex virus (HSV) has been reported to be associated with stromal keratitis, while the coxsackie virus has been reported to cause autoimmune myocarditis. Similarly, Theiler's murine encephalomyelitis virus causes demyelinating illness in animals. Furthermore, diabetic complications are linked to viral infections [15–18].

In addition to molecular mimicry, there is a mechanism of “bystander activation,” where a non-specific and highly reactive antiviral immune response in a localized pro-inflammatory milieu causes the release of self-antigens from injured tissue. These self-antigens activate autoreactive T lymphocytes, which induce inflammatory responses and contribute to autoimmunity [19,20]. A viral infection triggers the development of new self-antigens and autoreactive T or B cells, which then disseminate to target additional self-epitopes [21,22]. The spread of such epitopes has been described in individuals with rheumatic fever (RF), an autoimmune disease [23].

Bystander activation as well as molecular mimicry pathway involvement have been reported in autoimmune encephalomyelitis (EAE) models of MS, TMEV-IDD, and myasthenia gravis (MG) mediated by West Nile virus (WNV) [24–26]. Furthermore, T-cells that react to immune-dominant myelin basic protein (MBP) epitopes may cross-react with certain viral antigens, boosting the possibility of MS [27,28]. Serotype 4 of the Coxsackie B virus (CVB4) infection has been linked to T-cell specific autoimmune type 1 diabetes [29]. In CVB4-induced type 1 diabetes, both bystander activation and molecular mimicry mechanisms have been demonstrated [30,31]. Several studies in human and animal models have examined the role of rotaviruses in the development of autoimmune diabetes, suggesting that autoimmunity may be caused by bystanders [32,33]. Clinical studies have linked influenza infection to diabetes and other pancreatic diseases [34–39]. Herpesvirus and Epstein-Barr virus (EBV) infections are reported to be associated with the development of systemic autoimmune diseases (SADs). MS, RA, and Sjögren's syndrome (SS) are caused by EBV- and HSV-induced autoimmunity [2,40]. Other viruses, including measles, mumps, and rubella, are associated with the development of type 1 diabetes. Some of these viruses can infect and multiply in beta cells, causing autoimmune disorders [41,42].

Numerous hypotheses have been proposed to better understand the underlying processes of virus-induced autoimmunity; however, in most cases, a well-defined specific mechanism remains unclear. Despite the absence of a clear molecular explanation, multiple epidemiological and animal model experiments have shown that a broad spectrum of viruses may cause an autoimmune response. The emergence of autoimmune diseases after viral infection is a complicated process that is affected by several variables, including immune response, infectious dosage, and infection duration [43].

The viral and human proteins and their corresponding epitopes that share sequence and structural homology as well as exhibiting biochemical interactions with major histocompatibility complex (MHC) molecules may activate autoreactive T-cells, which eventually provoke autoimmune diseases. Currently, bioinformatics and immunoinformatics tools have gained considerable attention. These platforms facilitate the understanding of the complexity of peptide binding to different MHC molecules, forecasting cytokine release, and identifying the lead T- and B-cell epitopes [44,45]. We utilized the entire proteome

sequences of known human pathogenic virus species from different families, and the data were thoroughly examined in the context of the human proteome to identify potential sequence and structural homologs to prioritize virus-associated autoimmunity candidates. Several viral peptides have shown significant sequence and structural similarities to human peptides, and some of these homologs have been identified as promising T-cell epitopes that may be cross-reactive during the immune response. Knowledge of viral-human homologous proteins and peptides may be useful for understanding the molecular basis of virus-induced autoimmune diseases.

2. Results

2.1. Non-Paralogous Viral and Human Proteome Sets

The complete proteome sequences of the human pathogenic viruses available in the ViPR database were retrieved. These include viruses belonging to *Paramyxoviridae*, *Caliciviridae*, *Phenuiviridae*, *Flaviviridae*, *Hantaviridae*, *Pogaviridae*, *Hepeviridae*, *Filoviridae*, *Herpesviridae*, *nairoviridae*, *Arenaviridae*, *Peribunyaviridae*, *Poxviridae*, *Rhabdoviridae*, *Reoviridae*, *Coronaviridae*, Dengue viruses, Ebola viruses, Enteroviruses, Lassa viruses, and hepatitis C viruses. The compiled dataset is comprised of 129,191 protein sequences. In total, 74,468 non-redundant human proteins were retrieved from the NCBI database [46]. The viral protein sequences were subjected to CD-Hit clustering to remove paralogous sequences, with a threshold of 0.6. The resultant 68,322 non-paralogous viral protein sequences were utilised for downstream analysis.

2.2. Sequence Similarity Search

The BLASTp program was used to compare 68,322 non-paralogous viral proteins with the human proteome. A total of 24 viral-human homolog proteins were identified using comparative sequence analysis based on a bit-score ≥ 100 , query coverage ≥ 60 , percent identity ≥ 50 , and an E-value of 1×10^{-6} (Table 1).

Table 1. The top viral and human homolog proteins hits acquired from comparative proteome sequence analysis.

S. No	Query Sequence IDs	Subject Sequence IDs	Score	Query Coverage	Percent-Identity	E-Value
1	gb:AXN75085	sp P23921 RIR1_HUMAN	3148	98	75.297	0
2	gb:AST09466	sp P23921 RIR1_HUMAN	3130	100	73.106	0
3	gb:AEV80548	sp P35354 PGH2_HUMAN	2452	98	73.729	0
4	gb:AAY97564	sp P49916 DNLI3_HUMAN	1700	98	55.124	0
5	gb:AST09563	sp P49916 DNLI3_HUMAN	1594	99	51.852	0
6	gb:AZY90656	sp P31350 RIR2_HUMAN	1412	95	80.625	0
7	gb:AST09433	sp P31350 RIR2_HUMAN	1399	99	80.312	0
8	gb:QCA43223	sp P04818 TYSY_HUMAN	1162	95	71.579	2.94×10^{-161}
9	gb:BBA90853	sp P04818 TYSY_HUMAN	1153	89	69.333	2.63×10^{-159}
10	gb:AQY16903	sp Q9H2F3 3BHS7_HUMAN	834	99	50.559	9.70×10^{-110}
11	gb:ADZ29327	sp Q9HC24 LFG4_HUMAN	833	100	71.849	1.56×10^{-113}
12	gb:AZT86284	sp P07203 GPX1_HUMAN	831	83	84.153	6.52×10^{-114}
13	gb:AXN75107	sp P04183 KITH_HUMAN	656	97	69.006	1.45×10^{-87}
14	gb:AST09487	sp P04183 KITH_HUMAN	625	98	64.205	6.60×10^{-83}
15	gb:QCF48225	sp P22301 IL10_HUMAN	599	95	81.287	6.42×10^{-80}
16	gb:ABD28857	sp P00374 DYR_HUMAN	498	86	50	9.21×10^{-64}
17	gb:AAY97032	tr H0YNW5 H0YNW5_HUMAN	477	90	64.964	7.74×10^{-62}
18	gb:AUL80434	tr A0A0C4DGL3 A0A0C4DGL3_HUMAN	394	92	55.882	1.42×10^{-49}

Table 1. Cont.

S. No	Query Sequence IDs	Subject Sequence IDs	Score	Query Coverage	Percent-Identity	E-Value
19	gb:AUL80132	sp Q8IV08 PLD3_HUMAN	377	85	50.595	6.87×10^{-43}
20	gb:AA97407	sp Q9HC24 LFG4_HUMAN	367	97	63.248	9.72×10^{-45}
21	gb:AUL80484	sp P23921 RIR1_HUMAN	306	86	57.143	2.35×10^{-33}
22	gb:AUL80431	tr A0A3B3ITT3 A0A3B3ITT3_HUMAN	235	86	54.167	2.36×10^{-25}
23	gb:AEV80662	sp P09341 GROA_HUMAN	208	71	65.079	1.00×10^{-22}
24	gb:AEV80661	sp P19875 CXCL2_HUMAN	180	60	55.932	2.11×10^{-18}

2.3. Pathway Enrichment Analysis

The 24 viral protein sequences homologous to human proteins were subjected to pathway enrichment analysis using the PathDIP v4.0.7.0 database [47] for functional annotation. The metabolic pathways were manually compared to identify the proteins involved in the host and virus-shared pathways as well as virus-specific pathways. These pathways were filtered based on a *p*-value of <0.001 to identify significant hits (Table S1). Thirteen viral proteins were found to share pathways with nine human proteins, whereas eleven viral proteins were involved in virus-specific pathways. Most of the proteins are found to be involved in the autoimmune disease pathways, including cells and molecules involved in the local acute inflammatory response, TNF-related weak inducer of apoptosis (TWEAK) signaling, interleukin-11 signaling, p53 signaling, and inflammation mediated by chemokine and cytokine signaling.

2.4. Epitope Prediction

The immunogenic nature of proteins and peptides gives them the potential to bind to the MHC molecules with high binding affinities. MHC-I molecules are found in virtually all nucleated cells and precisely represent endogenous proteins or antigens processed by the cytosolic pathway, which represents cytotoxic T lymphocytes (CTLs). Exogenous antigens, usually the surface proteins of pathogens, are processed by endocytic processes and presented to T lymphocytes or CD4+ T cells [48]. Several algorithms and computational biology resources are available for predicting antigenic epitopes. In silico analysis revealed that pathogenic peptides exhibiting homology with their human counterparts have a significant binding capacity to MHC class-II molecules. Human host proteins with sequence homology to viral peptides may increase the susceptibility to autoimmunity. Epitopes with a binding score of $IC_{50} \leq 500$ nM were defined as HLA binders. The 23 most common HLA-DP, HLA-DQ, and HLA-DR alleles were utilized to predict the promiscuity of the mimicking peptides. Peptides with IC_{50} values ≤ 50 nM were speculated to be strong HLA-binders [45]. The epitopes with 15-mer peptide length and 9-mer core residues were prioritized downstream based on IC_{50} values ≤ 50 nM (Figure 1). The analyses eventually identified several promiscuous MHC class-II binding epitopes that demonstrated high binding affinity for all HLA alleles, with an $IC_{50} < 50$ nM. Several of these homolog epitopes were found to bind promiscuously to several HLA alleles, including HLA-DPA1*02:01/DPB1*05:01, HLA-DQA1*01:02/DQB1*06:02, HLA-DRB1*01:01, HLA-DPA1*01:03/DPB1*03:01, and HLA-DQA1*05:01/DQB1*03:01. The human leukocyte antigen DPB1 (HLA-DPB1) allele has been shown to influence the susceptibility and severity of rheumatoid arthritis. Numerous autoimmune diseases have been linked to HLADRB1-DQA1-DQB1 haplotype components encoded by HLA class-II alleles, including type-1 diabetes, Graves' disease, and RA [49]. Likewise, the DRB1*01:01 allele has been associated with autoimmune diseases such as rheumatoid arthritis [50]. The ability of the conserved regions to bind to class-II HLA alleles was assessed by docking the lead epitopes in the binding groove of HLA-DRB1, an allele known to predispose individuals to rheumatoid arthritis [51]. SLE and SS are associated with the DRB1*03:01 allele, whereas

autoimmune hepatitis (AIH) and RA are reported in association with the DRB1*04:05 allele [52].

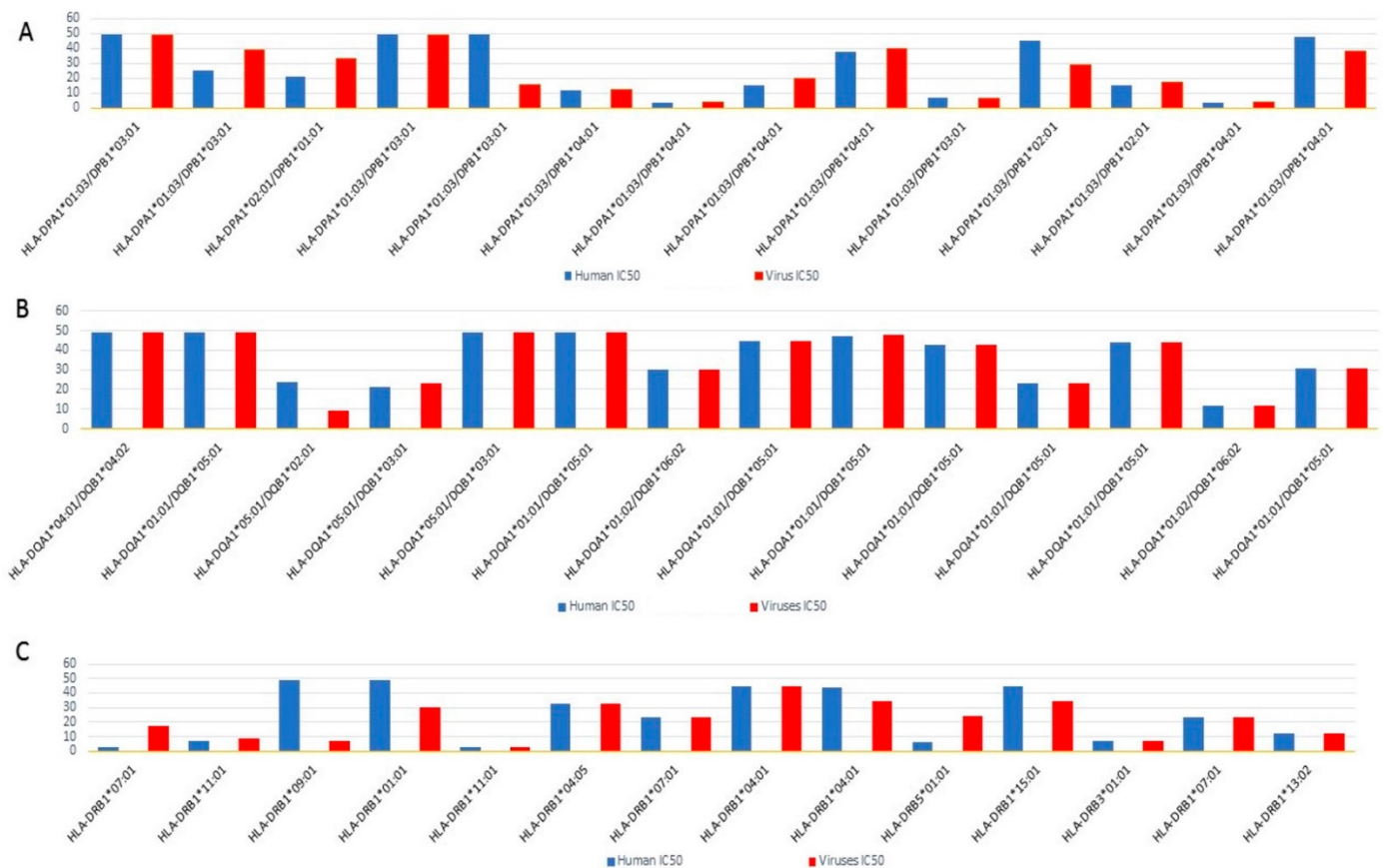


Figure 1. The viral-human mimicking epitopes' binding potential against HLA alleles, (A) HLA-DP; (B) HLA-DQ; and (C) HLA-DR. The plot represents the total number of binders for each allele. Strong binders ($IC_{50} \leq 50$), weak binders ($IC_{50} \leq 500$), and non-binders ($IC_{50} > 500$) were assigned to each fragment based on their expected IC_{50} values. The y-axis represents the IC_{50} values.

2.5. Molecular Mimicry Prediction of Viral-Human Homolog Epitopes

The trRosetta server [53] was used to estimate the three-dimensional structures of the viral-human homologous peptides. The resultant 3D structure's root mean square deviation (RMSD) was determined using the TM-Score web server with a threshold of 0–1. Viral-human homologous peptides with low RMSD values depicted a significant degree of structural mimicry. These homologous peptides were predicted to be the top candidates that may induce autoimmune diseases. Some peptides exhibited higher RMSD values than the set threshold; nevertheless, their structural resemblance was observed and prioritized.

2.6. Molecular Docking

Molecular docking analysis was performed to evaluate the MHC-II binding promiscuity of human and virus-mimicking peptides. Protein-protein rigid body docking was performed using the ClusPro server based on sampling billions of conformations, RMSD-based clustering, and energy minimization-based structural refinement [54]. Human and virus-mimicking peptides were subjected to molecular docking with human HLA (PDB ID: 5JLZ) and TLR4 (PDB ID: 3FXI) with default parameters. The docking results revealed that the homologous peptide epitopes interact feasibly with HLA and TLR4 receptor epitope-binding sites and develop multiple molecular interactions. The overall docking scores of these peptides within the immune receptors' antigen-binding sites were found to be significant (Figure 2; Table 2). Peptide fragments with the lowest energy scores showed the highest binding affinities (Supplementary Figures S1–S4). The molecular interactions of the

top prioritized viral-human identical epitope with the receptor protein-interacting residues are shown in Table S3.

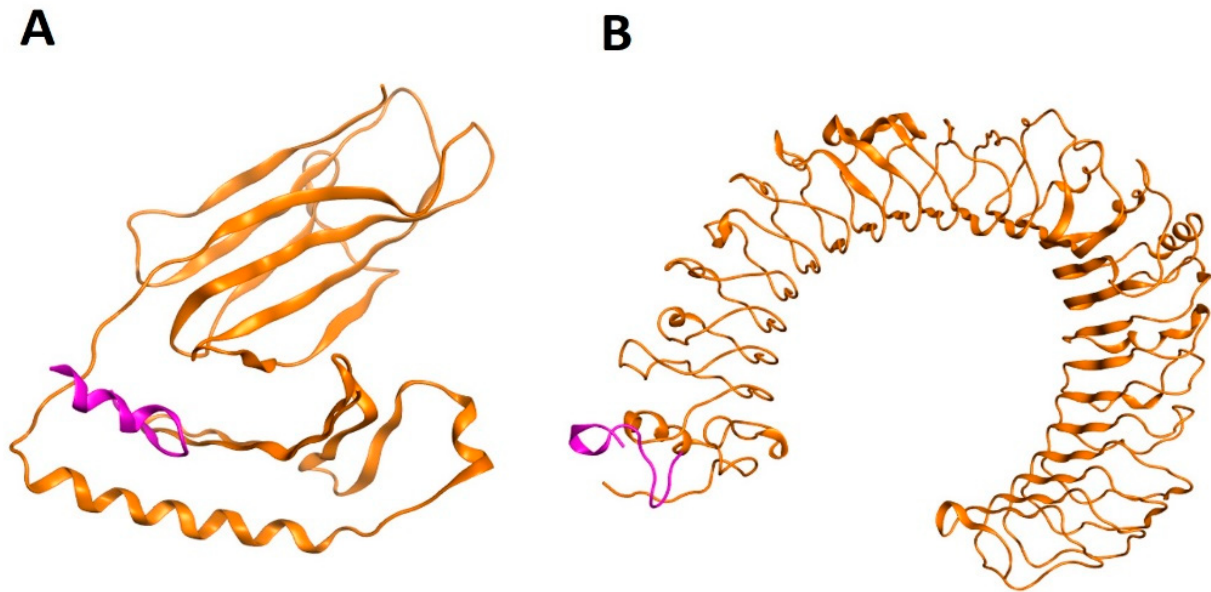


Figure 2. Molecular docking of the viral-human identical epitope (mentioned in S. No. 1, Table 2) with HLA (A) and TLR4 (B) receptors based on lowest binding energy. The purple colour indicates the top-prioritized peptide epitope, and the orange colour indicates the receptor proteins.

Table 2. Molecular docking scores of human and virus-mimicking peptides docked with the human HLA and TLR4 receptors. Viral-human homolog epitopes capable of binding to human host MHC class-II (":" denotes the distance between residue pairs).

S. No	Human Proteins	Human Peptides	Docking Score in Human HLA	Docking Score in Human TLR4	Virus Proteins	Virus Peptides	Docking Score in Human HLA	Docking Score in Human TLR4	Structural Mimicry	RMSD Value
1	Ribonucleoside-diphosphate reductase subunit M2	IFFSGSFASIFWLKK	−1105.4	−829.4	CPXV051	IFFSGSFASIFWLKK	−1105.4	−829.4	IFFSGSFASIFWLKK : : : : : : : : : : IFFSGSFASIFWLKK	0.00
2	Thymidine kinase, cytosolic	STELMRRVRRFQIAQ	−864	−689	thymidine kinase	STELIRRVRRYQIAQ	−853	−596.4	STELMRRVRRFQIAQ : : : : : : : : : : STELIRRVRRYQIAQ	0.1
3	Ribonucleoside-diphosphate reductase large subunit	RDFSYNFYGFKTLER	−854	−659.7	ribonucleotide reductase large subunit	RDFSYNFYGFKTLER	−854	−659.7	RDFSYNFYGFKTLER : : : : : : : : : : RDFSYNFYGFKTLER	0.1
4	Prostaglandin G/H synthase 2	MFAFFAQHFTHQFFK	−962	−742.8	prostaglandin G/H synthase 2	MFAFFAQHFTHQFFK	−962	−742.8	MFAFFAQHFTHQFFK : : : : : : : : : : MFAFFGQHFTHQFFR	0.1
5	Thymidylate synthase	TKRVFWKGVLEELLW	−962.9	−747	ORF13	TKRVFWRAVVEELLW	−117.6	−738	TKRVFWKGVLEELLW : : : : : : : : : : TKRVFWRAVVEELLW	0.2
6	Thymidylate synthase	VPFNIASYALLTYMI	−874.7	−613	ORF70	VPFNIASYSLTYML	−867	−745.6	VPFNIASYALLTYMI : : : : : : : : : : VPFNIASYSLTYML	0.3
7	Dihydrofolate reductase	RPLKGRINLVLSREL	−823	−1070	ORF2	RPLAGRINVVLSRTL	−1087	−782	RPLKGRINLVLSREL : : : : : : : : : : RPLAGRINVVLSRTL	0.8
8	DNA ligase 3	FVFDCIYFNDVSLMD	−951.7	−861	ATP-dependent DNA ligase	FVFDCIYFNDVSLMD	−951.7	−861	FVFDCIYFNDVSLMD : : : : : : : : : : FVFDCIYFNDVSLMD	0.9
9	thymidine kinase	LMRRVRRFQIAQYKC	−863.6	−691	thymidine kinase	LIRRVKRYQIAKYDC	−907	−652	LMRRVRRFQIAQYKC : : : : : : : : : : LIRRVKRYQIAKYDC	1
10	Ribonucleoside-diphosphate reductase large subunit	AGRRAAGASVATELR	−875.3	−781.9	ribonucleotide reductas	LMSLIAYCQSATELR	−917	−806.5	AGRRAAGASVATELR : : : : : : : : : : LMSLIAYCQSATELR	1.0

Table 2. Cont.

S. No	Human Proteins	Human Peptides	Docking Score in Human HLA	Docking Score in Human TLR4	Virus Proteins	Virus Peptides	Docking Score in Human HLA	Docking Score in Human TLR4	Structural Mimicry	RMSD Value
11	Growth-regulated alpha protein	IYDRDFSINYFGFK	−661	−602.4	chemokine vCXCL7	IINDRDFSINYFGFK	−789.5	−580.5	IYDRDFSINYFGFK :::~::~ IINDRDFSINYFGFK	1.0
12	C-X-C motif chemokine 2	LLVAASRAAGAPL	−763	−781	chemokine vCXCL6	SRLVATLLGTLLAC	−1006.9	−598	LLVAASRAAGAPL :::~::~ SRLVATLLGTLLAC	1.5
13	DNA ligase 3	CLVFDCIYFNDVSL	−820.4	−742.3	DNA ligase	CLVFDCLYFDGFDM	−942	−878	CLVFDCIYFNDVSL ::: ~:~::~ CLVFDCLYFDGFDM	2.1

3. Discussion

Autoimmune disorders (AID) are caused by an abnormal immune response that fails to distinguish between self and non-self antigens [1,2]. Molecular mimicry is based on the possibility that T- and B-cell antigenic determinants of pathogens may have a counterpart in the host and potentially cause autoimmunity [55]. We implemented an immunoinformatic platform to analyze a wide range of human-infecting viral proteins against the human proteome to prioritize the top hit epitopes that share sequence and 3D structural similarities. The top viral-human homolog peptide epitopes might be valuable targets to examine in association with autoimmune disorders, based on the concept of molecular mimicry. The analysis prioritized 13 viral peptides that showed significant amino acid sequences and 3D structural homologies with various human protein fragments. This includes one viral-human identical epitope that exhibited the highest docking score within the HLA and TLR4 immune receptors. Many of these homologous peptides exhibit promiscuous binding affinities to several MHC class-II molecules, which may provoke autoimmune disorders in humans.

Among the top viral-human mimic candidates, the human herpesvirus and poxvirus proteins exhibited significant 3D structural and sequence homology with human host proteins (Table S2). Several studies have reported that herpes simplex virus (HSV) is found in active plaques in the postmortem MS brain tissues of patients [56]. Additionally, the HSV-1 infection causes viral gene products to cause neural progenitor cells to undergo apoptosis [57]. The current molecular mimicry findings may help explain the molecular mechanisms underlying the onset of such an autoimmune disorder [54]. A study conducted by Bradshaw et al. (2015) reported herpes simplex virus 1 (HSV1)-induced encephalitis in association with voltage-gated calcium channel autoimmunity through a molecular mimicry mechanism [58].

Herpesvirus infections, particularly Epstein-Barr virus (EBV) infections, have been reported in many studies in association with several major autoimmune diseases [40,59]. We identified epitopic peptide homology between human interleukin-10 (IL-10) and gamma-herpesvirus 4 (HHV4). Human IL-10 is a major immune-regulatory cytokine that acts as a potent anti-inflammatory agent, affects a variety of immune cells, and prevents excessive tissue damage by inflammation [60]. Cytokines play a crucial role in the pathogenesis of autoimmune diseases. IL-10 is involved in the pathogenesis of autoimmune diseases, including RA, diabetes, and SLE [61,62]. We also noticed that the gamma herpesvirus 8 (HHV-8) ORF70 protein showed structural and sequence homology with the human TS peptide, and the HHV-8 ORF2 peptide is homologous to the human dihydrofolate reductase (DHFR) peptide. Early studies reported the presence of nine HHV-8 ORF gene products associated with autoimmunity and shared significant homology with human cellular proteins, including the HHV-8 TH and dihydrofolate reductase (DHFR) [63]. The human gammaherpes virus has been reported to be involved in the different systemic autoimmune diseases (SAD), where antibodies against ORFK8.1 were detected in SLS, SS, and vasculitis patients [64].

Significant sequence and structural homology was observed between cercopithecine betaherpesvirus 5 (CHV5) and human peptides in the current study. The prostaglandin G/H synthase 2 of CHV5 showed homology with the human prostaglandin G/H synthase 2 peptide. Human prostaglandin G/H synthase 2 (PTGS2) is involved in the biosynthesis of fibrous tissues, which eventually regulate immune responses during inflammation [65]. Likewise, the peptides of chemokine vCXCL7 from CHV5 showed sequence and 3D structural similarities to the epitopic peptides of the human growth-regulated alpha protein and C-X-C motif chemokine 2. Chemokines are primarily involved in leukocyte recruitment to sites of inflammation and have been reported to contribute to angiogenesis, tumor growth, and organ sclerosis [66].

The current study inferred that various strains of the Poxviridae family share substantial sequence and structural similarities with immunogenic peptides of human proteins. Viruses secrete an array of virus-encoding soluble cytokine receptors or cytokine analogs

that act as molecular decoys to inhibit the activity of host cytokines. The variety of poxvirus gene products systematically sabotage essential components of the inflammatory response and manipulate various intracellular signal transduction pathways that initiate proinflammatory responses. Numerous poxvirus genes that interfere with these pathways exhibit striking similarities with host immune system genes [67]. In our analysis, NY_014 poxvirus, monkeypox virus, cowpox virus, akhmeta virus, molluscum contagiosum virus, and vaccinia virus epitopes demonstrated striking resemblance to human proteome origin epitopes.

Metabolic pathways control lineage determination and immune system function, thereby affecting the onset of autoimmune disorders [68]. The majority of host-virus homologous proteins are involved in some of the most important autoimmune disease pathways, such as TNF-related weak inducer of apoptosis (TWEAK) signaling, cellular components involved in local acute inflammatory responses, IL-11 and IL6 signaling pathways, generic transcription pathways, p53 signaling, ataxia-telangiectasia mutated (ATM) signaling, and inflammation mediated by chemokine and cytokine signaling pathways.

The findings of the current study are based on immunoinformatic platforms and constrained prediction methods that may be uncertain due to conventional benchmarking, and a lack of precise datasets. The virus-human molecular mimic candidates prioritized in the current study, therefore, need additional validation via clinical and experimental approaches.

4. Materials and Methods

Structural bioinformatics and comparative sequence analysis platforms were followed in this study. The methodological workflow is shown in Figure 3.

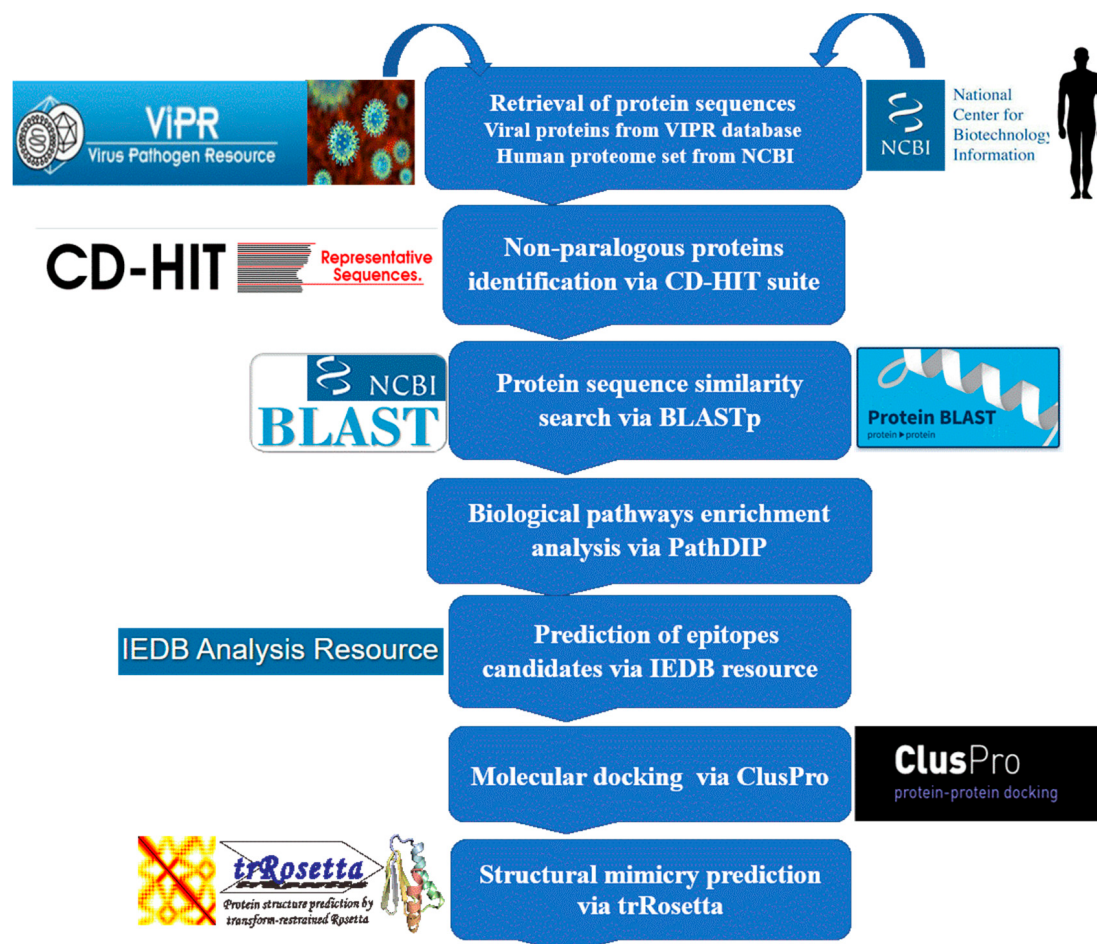


Figure 3. Systematic workflow diagram of autoimmune mimicry of viruses with human hosts, followed by T-cell epitope prediction, structural analysis, and molecular docking analysis.

4.1. Non-Paralogous Viral and Human Proteome Sequence Retrieval

Complete proteome sequences of all human pathogenic viruses were retrieved from the Virus Pathogen Database and Analysis Resource (ViPR) [69]. Redundant sequences were removed, and non-paralogous sequences were acquired using CD-HIT with a threshold of 0.9 (90% sequence similarity) for further analysis. CD-HIT uses a short-read filtering approach to cluster protein sequences with low redundancy [70]. Non-redundant human proteomic sets were retrieved from the NCBI database.

4.2. Sequence Similarity Search

A standalone version of the Basic Local Alignment Search Tool (BLAST) was used to compare the viral and human protein sequences [71]. Comparative sequence analyses using BLASTp were performed based on a cutoff e-value of 10^{-6} and a threshold of ≥ 100 bit score, $\geq 60\%$ query coverage, and $\geq 50\%$ sequence identity.

4.3. Metabolic Pathway Enrichment

The Path-DIP server was used for protein pathway enrichment analysis with a p -value < 0.0001 and other default parameters. The Path-DIP database is a curated reference of signaling cascades in human and non-human species that includes core pathways from major curated pathway databases as well as pathways predicted using orthology and physical protein interactions. The Path-DIP provides access to both computationally predicted and experimentally confirmed protein–protein interactions (PPIs) [47].

4.4. Epitope Candidate Prediction

The viral-human homolog protein epitopes bound to the MHC-II were predicted using the Immune Epitope Database (IEDB) [72]. The NN-align-2.2 (NetMHCII-2.2) approach predicted binding peptides with multiple human HLA class II alleles, DR, DQ, and HLA-DP, with half-maximal inhibitory concentration (IC_{50}) cutoff values of less than 50 nM. Peptides with IC_{50} values less than 50 nM were considered highly compatible binders. The enriched proteins in the metabolic pathways and their respective homologs were subjected to IEDB by selecting HLA class-II binding alleles (Table 3).

Table 3. The HLA class-II binding alleles selected in the current study based on an IC_{50} value < 50 nM.

S/No	HLA-DP	HLA-DQ	HLA-DR
1	DPA1*01:03-DPB1*02:01	DQA1*01:02-DQB1*06:02	DRB1*03:01
2	DPA1*02:01-DPB1*05:01	-DQA1*04:01-DQB1*04:02	DRB1*04:04
3	DPA1*03:01-DPB1*04:02	DQA1*05:01-DQB1*03:01	DRB1*07:01
4	DPA1*01:03-DPB1*04:01	DQA1*01:01-DQB1*05:01	DRB1*11:01
5	DPA1*01:03-DPB1*03:01-DPB1*04:01	DQA1*05:01-DQB1*03:01	DRB1*13:02
			DRB3*01:01
			DRB5*01:01
			DRB1*01:01
			DRB4*01:01
6	DPA1*02:01-DPB1*01:01	DQA1*03:01-DQB1*03:02	DRB1*04:01
			DRB1*15:01
			DRB1*04:05
			DRB1*11:01
			DRB1*08:02

4.5. Molecular Modeling and Docking Analyses

The 3D structures of the top viral-human homolog peptide epitopes were docked against the human leukocyte antigen (HLA) and toll-like receptor 4 (TLR4) immune receptors. The protein 3D structure data for HLA and TLR4 were acquired from the Protein Data Bank (PDB) via the 5JLZ and 3FXI PDB IDs, respectively. The peptide epitope 3D structures were modeled using the UCSF Chimera programme [73]. The ClusPro server was used to calculate the binding potential of the epitopic peptides to human HLA and TLR4 immune receptors. The ClusPro server generates different models based on binding energies [54].

4.6. Structural Mimicry Prediction

The trRosetta server was used to predict the 3D structures of the peptides. The trRosetta server (transform-restrained Rosetta) is a web-based tool that accurately predicts protein and peptide structures. trRosetta is one of the most accurate methods for estimating the 3D structure of molecules via ab initio-based simulations [74]. The 3D structure prediction process in trRosetta is based on energy minimization, with constraints derived from the predicted inter-residue distance and orientations [53]. A template modeling (TM) score was used to measure the structural similarity of the peptides based on the root mean square deviation (RMSD).

5. Conclusions

Comparative sequence analyses and immunoinformatics approaches were employed in the current study to uncover sequence- and structure-based molecular mimics of viral-human proteins as possible autoimmune candidates. BLASTp analysis identified 24 viral proteins with significant sequence homology to human host proteins. Biological pathway enrichment analysis revealed the involvement of viral-human homolog proteins in a variety of human metabolic pathways. Immune epitope prediction analysis inferred that the viral-human homolog proteins shared 13 promising T-cell epitopes, suggesting promiscuous binding to human HLA class II alleles. The experimental validation of these proteins and their top-hit host-pathogen homolog epitopes may explain the virus-based autoimmune diseases in humans.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/pathogens11111362/s1>, Figure S1: Molecular docking results of mimicking human peptides docked with HLA receptor; Figure S2: Molecular docking results of mimicking human peptides docked with TLR4 receptor; Figure S3: Molecular docking results of mimicking viral peptides docked with HLA receptor; Figure S4: Molecular docking results of mimicking viral peptides docked with TLR4 receptor; Table S1: Viral-human homologs proteins metabolic pathways enrichment analysis; Table S2: Viral proteins homologous with human proteins sharing homologous epitopes. Table S3: The hydrogen bonding interaction between the top ranked virus-human molecular mimic epitope and HLA and TLR receptors residues. The interactions was identified by molecular docking of epitope within HLA and TLR4 receptors.

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References

1. Ercolini, A.M.; Miller, S.D. The role of infections in autoimmune disease. *Clin. Exp. Immuno.* **2009**, *155*, 1–15. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Smatti, M.K.; Cyprian, F.S.; Nasrallah, G.K.; Al Thani, A.A.; Almishal, R.O.; Yassine, H.M. Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms. *Viruses* **2019**, *11*, 762. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Selgrade, M.K.; Cooper, G.S.; Germolec, D.R.; Heindel, J.J. Linking environmental agents and autoimmune disease: An agenda for future research. *Environ. Health Perspect.* **1999**, *107*, 811–813.
4. Casiraghi, C.; Shanina, I.; Cho, S.; Freeman, M.L.; Blackman, M.A.; Horwitz, M.S. Gammaherpesvirus Latency Accentuates EAE Pathogenesis: Relevance to Epstein-Barr Virus and Multiple Sclerosis. *PLoS Pathogens*. **2012**, *8*, e1002715. [\[CrossRef\]](#)
5. Pahari, S.; Chatterjee, D.; Negi, S.; Kaur, J.; Singh, B.; Agrewala, J.N. Morbid Sequences Suggest Molecular Mimicry between Microbial Peptides and Self-Antigens: A Possibility of Inciting Autoimmunity. *Front. Microbiol.* **2017**, *8*, 1938. [\[CrossRef\]](#)
6. Arleevskaya, M.I.; Manukyan, G.; Inoue, R.; Aminov, R. Editorial: Microbial and Environmental Factors in Autoimmune and Inflammatory Diseases. *Front. Immunol.* **2017**, *8*, 243. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Finnegan, A.; Needleman, B.W.; Hodes, R.J. Function of Autoreactive T Cells in Immune Responses. *Immunol. Rev.* **1990**, *116*, 15–31. [\[CrossRef\]](#) [\[PubMed\]](#)
8. Wang, P.; Zheng, S.G. Regulatory T cells and B cells: Implication on autoimmune diseases. *Int. J. Clin. Exp. Pathol.* **2013**, *6*, 2668–2674.
9. Curran, S.A.; Hollan, I.; Erridge, C.; Lappin, D.F.; Murray, C.A.; Sturfelt, G.; Mikkelsen, K.; Førre, O.T.; Almdahl, S.M.; Fagerhol, M.K.; et al. Bacteria in the Adventitia of Cardiovascular Disease Patients with and without Rheumatoid Arthritis. *PLoS ONE* **2014**, *9*, e98627. [\[CrossRef\]](#)
10. Rioux, J.D.; Abbas, A.K. Paths to understanding the genetic basis of autoimmune disease. *Nature* **2005**, *435*, 584–589. [\[CrossRef\]](#)
11. Mohammed, J.P.; Fusakio, M.E.; Rainbow, D.B.; Moule, C.; Fraser, H.I.; Clark, J.; Todd, J.A.; Peterson, L.B.; Savage, P.B.; Wills-Karp, M.; et al. Identification of Cd101 as a susceptibility gene for *Novosphingobium aromaticivorans*-induced liver autoimmunity. *J. Immunol.* **2011**, *187*, 337. [\[CrossRef\]](#) [\[PubMed\]](#)
12. Lleo, A.; Bowlus, C.L.; Yang, G.X.; Invernizzi, P.; Podda, M.; Van de Water, J.; Ansari, A.A.; Coppel, R.L.; Worman, H.J.; Gores, G.J.; et al. Biliary apoptoses and anti-mitochondrial antibodies activate innate immune responses in primary biliary cirrhosis. *Hepatology* **2010**, *52*, 987–998. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Kim, B.; Kaistha, S.D.; Rouse, B.T. Viruses and autoimmunity. *Autoimmunity* **2006**, *39*, 71–77. [\[CrossRef\]](#)
14. Rojas, M.; Restrepo-Jiménez, P.; Monsalve, D.M.; Pacheco, Y.; Acosta-Ampudia, Y.; Ramírez-Santana, C.; Leung, P.S.C.; Ansari, A.A.; Gershwin, M.E.; Anaya, J.M. Molecular mimicry and autoimmunity. *J. Autoimmun.* **2018**, *95*, 100–123. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Zhao, Z.S.; Granucci, F.; Yeh, L.; Schaffer, P.A.; Cantor, H. Molecular mimicry by herpes simplex virus-type 1: Autoimmune disease after viral infection. *Science* **1998**, *279*, 1344–1347. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Coppieters, K.T.; Wiberg, A.; von Herrath, M.G. Viral infections and molecular mimicry in type 1 diabetes. *Apmis* **2012**, *120*, 941–949. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Gauntt, C.J.; Arizpe, H.M.; Higdon, A.L.; Wood, H.J.; Bowers, D.F.; Rozek, M.M.; Crawley, R. Molecular mimicry, anti-coxsackievirus B3 neutralizing monoclonal antibodies, and myocarditis. *J. Immunol.* **1995**, *154*, 2983–2995.
18. Getts, D.R.; Chastain, E.M.; Terry, R.L.; Miller, S.D. Virus infection, antiviral immunity, and autoimmunity. *Immunol. Rev.* **2013**, *255*, 197–209. [\[CrossRef\]](#)
19. Fujinami, R.S.; von Herrath, M.G.; Christen, U.; Whitton, J.L. Molecular mimicry, bystander activation, or viral persistence: Infections and autoimmune disease. *Clin. Microbiol. Rev.* **2006**, *19*, 80–94. [\[CrossRef\]](#)
20. Kivity, S.; Agmon-Levin, N.; Blank, M.; Shoenfeld, Y. Infections and autoimmunity—Friends or foes? *Trends Immunol.* **2009**, *30*, 409–414. [\[CrossRef\]](#)
21. Vanderlugt, C.L.; Miller, S.D. Epitope spreading in immune-mediated diseases: Implications for immunotherapy. *Nat. Rev. Immunol.* **2002**, *2*, 85–95. [\[CrossRef\]](#) [\[PubMed\]](#)
22. Olson, J.K.; Croxford, J.L.; Miller, S.D. Virus-Induced Autoimmunity: Potential Role of Viruses in Initiation, Perpetuation, and Progression of T-Cell-Mediated Autoimmune Disease. *Viral Immunol.* **2001**, *14*, 227–250. [\[CrossRef\]](#) [\[PubMed\]](#)
23. Garcia, A.F.; Yamaga, K.M.; Shafer, L.A.; Bollt, O.; Tam, E.K.; Cunningham, M.W.; Kurahara, D.K. Cardiac Myosin Epitopes Recognized by Autoantibody in Acute and Convalescent Rheumatic Fever. *Pediatr. Infect. Dis. J.* **2016**, *35*, 1021–1026. [\[CrossRef\]](#) [\[PubMed\]](#)
24. Constantinescu, C.S.; Farooqi, N.; O'Brien, K.; Gran, B. Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). *Br. J. Pharmacol.* **2011**, *164*, 1079–1106. [\[CrossRef\]](#)
25. Leis, A.A.; Szatmary, G.; Ross, M.A.; Stokic, D.S. West Nile virus infection and myasthenia gravis. *Muscle Nerve* **2014**, *49*, 26–29. [\[CrossRef\]](#)

26. Miller, S.D.; Vanderlugt, C.L.; Begolka, W.S.; Pao, W.; Yauch, R.L.; Neville, K.L.; Katz-Levy, Y.; Carrizosa, A.; Kim, B.S. Persistent infection with Theiler's virus leads to CNS autoimmunity via epitope spreading. *Nat. Med.* **1997**, *3*, 1133–1136. [\[CrossRef\]](#)
27. Liebert, U.G.; Linington, C.; ter Meulen, V. Induction of autoimmune reactions to myelin basic protein in measles virus encephalitis in Lewis rats. *J. Neuroimmunol.* **1988**, *17*, 103–118. [\[CrossRef\]](#)
28. Martinsen, V.; Kursula, P. Multiple sclerosis and myelin basic protein: Insights into protein disorder and disease. *Amino Acids* **2022**, *54*, 99–109. [\[CrossRef\]](#)
29. Filippi, C.M.; von Herrath, M.G. Viral trigger for type 1 diabetes: Pros and cons. *Diabetes* **2008**, *57*, 2863–2871. [\[CrossRef\]](#)
30. Kaufman, D.L.; Erlander, M.G.; Clare-Salzler, M.; Atkinson, M.A.; Maclaren, N.K.; Tobin, A.J. Autoimmunity to two forms of glutamate decarboxylase in insulin-dependent diabetes mellitus. *J. Clin. Investig.* **1992**, *89*, 283–292. [\[CrossRef\]](#)
31. Pane, J.A.; Coulson, B.S. Lessons from the mouse: Potential contribution of bystander lymphocyte activation by viruses to human type 1 diabetes. *Diabetologia* **2015**, *58*, 1149–1159. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Honeyman, M.C.; Coulson, B.S.; Stone, N.L.; Gellert, S.A.; Goldwater, P.N.; Steele, C.E.; Couper, J.J.; Tait, B.D.; Colman, P.G.; Harrison, L.C. Association between rotavirus infection and pancreatic islet autoimmunity in children at risk of developing type 1 diabetes. *Diabetes* **2000**, *49*, 1319–1324. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Pane, J.A.; Webster, N.L.; Coulson, B.S. Rotavirus activates lymphocytes from non-obese diabetic mice by triggering toll-like receptor 7 signaling and interferon production in plasmacytoid dendritic cells. *PLoS Pathog.* **2014**, *10*, e1003998. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Roman, L.M.; Simons, L.F.; Hammer, R.E.; Sambrook, J.F.; Gething, M.J. The expression of influenza virus hemagglutinin in the pancreatic beta cells of transgenic mice results in autoimmune diabetes. *Cell* **1990**, *61*, 383–396. [\[CrossRef\]](#)
35. Tan, H.; Wang, C.; Yu, Y. H1N1 influenza: The trigger of diabetic ketoacidosis in a young woman with ketosis-prone diabetes. *Am. J. Med. Sci.* **2012**, *343*, 180–183. [\[CrossRef\]](#)
36. Capua, I.; Mercalli, A.; Pizzuto, M.S.; Romero-Tejeda, A.; Kasloff, S.; De Battisti, C.; Bonfante, F.; Patrono, L.V.; Vicenzi, E.; Zappulli, V.; et al. Influenza A viruses grow in human pancreatic cells and cause pancreatitis and diabetes in an animal model. *J. Virol.* **2013**, *87*, 597–610. [\[CrossRef\]](#)
37. Oughton, M.; Dascal, A.; Laporta, D.; Charest, H.; Afilalo, M.; Miller, M. Evidence of viremia in 2 cases of severe pandemic influenza A H1N1/09. *Diagn. Microbiol. Infect. Dis.* **2011**, *70*, 213–217. [\[CrossRef\]](#)
38. Lönnrot, M.; Lynch, K.F.; Elding Larsson, H.; Lernmark, Å.; Rewers, M.J.; Törn, C.; Burkhardt, B.R.; Briese, T.; Hagopian, W.A.; She, J.X.; et al. Respiratory infections are temporally associated with initiation of type 1 diabetes autoimmunity: The TEDDY study. *Diabetologia* **2017**, *60*, 1931–1940. [\[CrossRef\]](#)
39. Luo, G.; Ambati, A.; Lin, L.; Bonvalet, M.; Partinen, M.; Ji, X.; Maecker, H.T.; Mignot, E.J. Autoimmunity to hypocretin and molecular mimicry to flu in type 1 narcolepsy. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, e12323–e12332. [\[CrossRef\]](#)
40. Draborg, A.H.; Duus, K.; Houen, G. Epstein-Barr virus and systemic lupus erythematosus. *Clin. Dev. Immunol.* **2012**, *2012*, 370516. [\[CrossRef\]](#)
41. Numazaki, K.; Goldman, H.; Seemayer, T.A.; Wong, I.; Wainberg, M.A. Infection by human cytomegalovirus and rubella virus of cultured human fetal islets of Langerhans. *In Vivo* **1990**, *4*, 49–54.
42. Ramondetti, F.; Sacco, S.; Comelli, M.; Bruno, G.; Falorni, A.; Iannilli, A.; d'Annunzio, G.; Iafusco, D.; Songini, M.; Toni, S.; et al. Type 1 diabetes and measles, mumps and rubella childhood infections within the Italian Insulin-dependent Diabetes Registry. *Diabet Med.* **2012**, *29*, 761–766. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Christen, U.; von Herrath, M.G. Do viral infections protect from or enhance type 1 diabetes and how can we tell the difference? *Cell Mol. Immunol.* **2011**, *8*, 193–198. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Korber, B.; LaBute, M.; Yusim, K. Immunoinformatics comes of age. *PLoS Comput. Biol.* **2006**, *2*, e71. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Tomar, N.; De, R.K. Immunoinformatics: An integrated scenario. *Immunology* **2010**, *131*, 153–168. [\[CrossRef\]](#) [\[PubMed\]](#)
46. NCBI Resource Coordinators. Database resources of the National Center for Biotechnology Information. *Nucleic Acids Res.* **2013**, *41*, D8–D20.
47. Rahmati, S.; Abovsky, M.; Pastrello, C.; Kotlyar, M.; Lu, R.; Cumbaa, C.A.; Rahman, P.; Chandran, V.; Jurisica, I. pathDIP 4: An extended pathway annotations and enrichment analysis resource for human, model organisms and domesticated species. *Nucleic Acids Res.* **2020**, *48*, D479–D488. [\[CrossRef\]](#)
48. Ahmed, R.K.S.; Maeurer, M.J. T-cell epitope mapping. *Methods Mol. Biol.* **2009**, *524*, 427–438.
49. Bernecker, C.; Ostapczuk, M.; Vordenbümen, S.; Ehlers, M.; Thiel, A.; Schinner, S.; Willenberg, H.; Scherbaum, W.A.; Schott, M. HLA-A2 phenotype may be protective against Graves' disease but not against Hashimoto's thyroiditis in Caucasians. *Horm. Metab. Res.* **2013**, *45*, 74–77. [\[CrossRef\]](#)
50. Jiang, L.; Jiang, D.; Han, Y.; Shi, X.; Ren, C. Association of HLA-DPB1 polymorphisms with rheumatoid arthritis: A systemic review and meta-analysis. *Int. J. Surg.* **2018**, *52*, 98–104. [\[CrossRef\]](#)
51. Venigalla, S.S.K.; Premakumar, S.; Janakiraman, V. A possible role for autoimmunity through molecular mimicry in alphavirus mediated arthritis. *Sci Rep.* **2020**, *10*, 938. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Zanelli, E.; Breedveld, F.C.; de Vries, R.R. HLA association with autoimmune disease: A failure to protect? *Rheumatology* **2000**, *39*, 1060–1066. [\[CrossRef\]](#) [\[PubMed\]](#)
53. Du, Z.; Su, H.; Wang, W.; Ye, L.; Wei, H.; Peng, Z.; Anishchenko, I.; Baker, D.; Yang, J. The trRosetta server for fast and accurate protein structure prediction. *Nat. Protoc.* **2021**, *16*, 5634–5651. [\[CrossRef\]](#) [\[PubMed\]](#)

54. Kozakov, D.; Hall, D.R.; Xia, B.; Porter, K.A.; Padhorny, D.; Yueh, C.; Beglov, D.; Vajda, S. The ClusPro web server for protein–protein docking. *Nat. Protoc.* **2017**, *12*, 255–278. [\[CrossRef\]](#)
55. Cusick, M.F.; Libbey, J.E.; Fujinami, R.S. Molecular mimicry as a mechanism of autoimmune disease. *Clin. Rev. Allergy Immunol.* **2012**, *42*, 102–111.
56. Sanders, V.J.; Waddell, A.E.; Felisan, S.L.; Li, X.; Conrad, A.J.; Tourtellotte, W.W. Herpes simplex virus in postmortem multiple sclerosis brain tissue. *Arch. Neurol.* **1996**, *53*, 125–133. [\[CrossRef\]](#)
57. Chucair-Elliott, A.J.; Conrady, C.; Zheng, M.; Kroll, C.M.; Lane, T.E.; Carr, D.J. Microglia-induced IL-6 protects against neuronal loss following HSV-1 infection of neural progenitor cells. *Glia* **2014**, *62*, 1418–1434. [\[CrossRef\]](#)
58. Bradshaw, M.J.; Pawate, S.; Lennon, V.A.; Bloch, K.C.; Brown, K.M. Herpes simplex virus 1 encephalitis associated with voltage-gated calcium channel autoimmunity. *Neurology* **2015**, *85*, 2176–2177. [\[CrossRef\]](#)
59. Yu, S.F.; Wu, H.C.; Tsai, W.C.; Yen, J.H.; Chiang, W.; You, C.Y.; Lu, S.N.; Chiang, L.C.; Chen, C.J. Detecting Epstein-Barr virus DNA from peripheral blood mononuclear cells in adult patients with systemic lupus erythematosus in Taiwan. *Med. Microbiol. Immunol.* **2005**, *194*, 115–120. [\[CrossRef\]](#)
60. Yoon, S.I.; Logsdon, N.J.; Sheikh, F.; Donnelly, R.P.; Walter, M.R. Conformational changes mediate interleukin-10 receptor 2 (IL-10R2) binding to IL-10 and assembly of the signaling complex. *J. Biol. Chem.* **2006**, *281*, 35088–35096. [\[CrossRef\]](#)
61. Sun, L.; Louie, M.C.; Vannella, K.M.; Wilke, C.A.; LeVine, A.M.; Moore, B.B.; Shanley, T.P. New concepts of IL-10-induced lung fibrosis: Fibrocyte recruitment and M2 activation in a CCL2/CCR2 axis. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2011**, *300*, L341–L353. [\[CrossRef\]](#) [\[PubMed\]](#)
62. Moudgil, K.D.; Choubey, D. Cytokines in autoimmunity: Role in induction, regulation, and treatment. *J. Interferon. Cytokine Res.* **2011**, *31*, 695–703. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Nicholas, J.; Ruvolo, V.; Zong, J.; Ciufo, D.; Guo, H.G.; Reitz, M.S.; Hayward, G.S. A single 13-kilobase divergent locus in the Kaposi sarcoma-associated herpesvirus (human herpesvirus 8) genome contains nine open reading frames that are homologous to or related to cellular proteins. *J. Virol.* **1997**, *71*, 1963–1974. [\[CrossRef\]](#) [\[PubMed\]](#)
64. Balada, E.; Ramentol, M.; Felip, L.; Ordi-Ros, J.; Selva-O’Callaghan, A.; Simeón-Aznar, C.P.; Solans-Laqué, R.; Vilardell-Tarrés, M. Prevalence of HHV-8 in systemic autoimmune diseases. *J. Clin. Virol.* **2015**, *62*, 84–88. [\[CrossRef\]](#) [\[PubMed\]](#)
65. Levin, G.; Duffin, K.L.; Obukowicz, M.G.; Hummert, S.L.; Fujiwara, H.; Needleman, P.; Raz, A. Differential metabolism of dihomo-gamma-linolenic acid and arachidonic acid by cyclo-oxygenase-1 and cyclo-oxygenase-2: Implications for cellular synthesis of prostaglandin E1 and prostaglandin E2. *Biochem. J.* **2002**, *365*, 489–496. [\[CrossRef\]](#) [\[PubMed\]](#)
66. Rotondi, M.; Chiovato, L.; Romagnani, S.; Serio, M.; Romagnani, P. Role of chemokines in endocrine autoimmune diseases. *Endocr. Rev.* **2007**, *28*, 492–520. [\[CrossRef\]](#) [\[PubMed\]](#)
67. Seet, B.T.; Johnston, J.B.; Brunetti, C.R.; Barrett, J.W.; Everett, H.; Cameron, C.; Sypula, J.; Nazarian, S.H.; Lucas, A.; McFadden, G. Poxviruses and immune evasion. *Annu. Rev. Immunol.* **2003**, *21*, 377–423. [\[CrossRef\]](#) [\[PubMed\]](#)
68. Huang, N.; Perl, A. Metabolism as a Target for Modulation in Autoimmune Diseases. *Trends Immunol.* **2018**, *39*, 562–576. [\[CrossRef\]](#)
69. Pickett, B.E.; Sadat, E.L.; Zhang, Y.; Noronha, J.M.; Squires, R.B.; Hunt, V.; Liu, M.; Kumar, S.; Zaremba, S.; Gu, Z.; et al. ViPR: An open bioinformatics database and analysis resource for virology research. *Nucleic Acids Res.* **2012**, *40*, D593–D598. [\[CrossRef\]](#)
70. Huang, Y.; Niu, B.; Gao, Y.; Fu, L.; Li, W. CD-HIT Suite: A web server for clustering and comparing biological sequences. *Bioinformatics* **2010**, *26*, 680–682. [\[CrossRef\]](#)
71. Johnson, M.; Zaretskaya, I.; Raytselis, Y.; Merezuk, Y.; McGinnis, S.; Madden, T.L. NCBI BLAST: A better web interface. *Nucleic Acids Res.* **2008**, *36*, W5–W9. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Fleri, W.; Paul, S.; Dhanda, S.K.; Mahajan, S.; Xu, X.; Peters, B.; Sette, A. The Immune Epitope Database and Analysis Resource in Epitope Discovery and Synthetic Vaccine Design. *Front. Immunol.* **2017**, *8*, 278. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Pettersen, E.F.; Goddard, T.D.; Huang, C.C.; Couch, G.S.; Greenblatt, D.M.; Meng, E.C.; Ferrin, T.E. UCSF Chimera—a visualization system for exploratory research and analysis. *J. Comput. Chem.* **2004**, *25*, 1605–1612. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Rahman, N.; Begum, S.; Khan, A.; Afridi, S.G.; Khayam Sahibzada, M.U.; Atwah, B.; Alhindi, Z.; Khan, H. An insight in Salmonella typhi associated autoimmunity candidates’ prediction by molecular mimicry. *Comput. Biol. Med.* **2022**, *148*, 105865. [\[CrossRef\]](#) [\[PubMed\]](#)