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The Antifungal Effect of Di-Acetyl Produced by Isolated Lactobacilli from Traditional Dairy Products

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Abstract

Almost all autoimmune diseases (AD) have been associated with at least one infection. Multidrug-resistant *Acinetobacter baumannii* is classified by the WHO and CDC as a critical-priority pathogen. In this study, the proteome of *A. baumannii* ATCC1906 was investigated regarding the potential to cause AD. First, the protein sequences of *A. baumannii* were subjected to NCBI BLASTp with an E-value threshold of $\leq 1\times10^{-6}$ against the *Homo sapiens* proteome to find sequences with ≥9 amino acid similarities. Then, the association of human proteins, which possessed similar bacterial peptides, in the development of ADs was evaluated by the Autoimmune Disease Association Database (GAAD). Next, peptides of AD-associated proteins were checked for their ability to bind to MHCI and MHCII molecules, and the population coverage of alleles binding to potent peptides was extracted. The results indicated that ninety-four proteins from this bacterium had identical peptide sequences with 957 human AD-related proteins. Among 213 peptides, 12 peptide sequences have the possibility of strong binding with MHCI (%Rank < 0.5), and 13 peptide sequences have the possibility of strong binding with MHCII (%Rank < 2). CEAHLGHVF and QIQGFFDIPVDN established the strongest connections with MHCI and MHCII. YVGAGTVEF peptide could also bind to both MHC classes. Regarding the peptides binding the alleles with the highest population coverages, GAEPLFFLDY (world coverage of 17.34%) and LPGAGGTQRL (world coverage of 12.78%) were the top MHCI and MHCII binding peptides. These findings suggest candidate peptides that meet the first checkpoint of molecular mimicry, warranting experimental evaluation for potential links to immune-mediated and autoimmune conditions, including Parkinson's disease, Vitiligo, Inflammatory bowel disease, Systemic lupus erythematosus, Rheumatoid arthritis, Multiple sclerosis, Antiphospholipid syndrome, and IgA nephropathy.

1. Introduction

Autoimmune Diseases (AD) are the third cause of mortality in industrial countries, following cancer and cardiovascular diseases (Kivity *et al.*, 2009). Studies indicate that approximately 3% of the European and North American populations suffer from some ADs; in addition, it has been shown that there is a discrepancy in AD's sex distribution, with 75% of people suffering from AD being women. Some of the most common ADs include insulin-dependent diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, thyroiditis, multiple sclerosis, arteriosclerosis, and inflammatory bowel disease (Smith & Germolec, 1999). Bi-directional responses between bacterial species and autoantigens have long been proven to affect AD development in susceptible individuals (Tsokos, 2020).

A prominent theory suggests that some microorganisms prevent the development of inflammatory diseases, and thus, their loss leads to an increase in the prevalence of allergies, asthma, and ADs (Akdis, 2021). It is further backed up by the observation that in both patients suffering from AD and animal models, the development of AD commonly occurs alongside infection.

Furthermore, it has been seen that AD develops following an infection. In most of these cases, no trace of microorganisms is observed during and after the development, indicating the cause is not the direct effect of infection but rather the host's immune responses initiated by microbes becoming dysregulated (Christen, 2018). ADs are primarily caused by immune system dysregulation and failure in host-pathogen cell recognition by cells involved in the immune response (Smith & Germolec, 1999).

Multiple factors interplay in AD development, namely genetics, immunogenic, hormonal, and environmental, have led to the term "immunologic musaism" to describe multi-factorial interplays (Kivity *et al.*, 2009). Three

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primary mechanisms are involved in the development of ADs: Bystander activation, a mechanism in which Antigen-Presenting Cells (APCs) are activated by infection and, in turn, activate bystanders, producing inflammatory cytokines (Pan *et al.*, 2019).

Molecular mimicry, in which bacterial antigens are similar to the autoantigens, leads to host intolerance (Cunningham, 2019). Finally, Epitope spreading happens when an autoimmune response that starts by targeting one self-epitope later broadens to hit more epitopes on the same or different proteins.

This happens because tissue damage lets out hidden autoantigens. These then get presented to naive T cells, which amps up and keeps the autoimmunity going (Johnson & Jiang, 2023).

One of the most infamous causes of bacterial infection is multi-drug resistant (MDR) *Acinetobacter baumannii*. *Acinetobacter* strains include Gram-negative coccobacillus bacteria, most being nonpathogenic, although *A. baumanni*, *A. calcoaceticus*, and *A. lwoffii* are pathogenic and known to be present in water, soil, and healthcare facilities (Guerrero *et al.*, 2010). *A. baumannii* has become a primary worldwide concern; the Centers for Disease Control and Prevention (CDC) has categorized it as a serious threat and top priority (Pires & Parker, 2019). *A. baumanni* can persist in stressful environments and is a major contributor to hospital-borne diseases; moreover, *A. baumannii* exhibits resistance to most antibiotics, including carbapenems.

Even colistin and tigecycline — previously considered last-resort agents — are now facing emerging resistance worldwide (Antunes *et al.*, 2014; Davis *et al.*, 2005; Freire *et al.*, 2016; Peleg et al, 2008; Raro et al, 2017; Jo *et al.*, 2023).

ADs can be divided into two main groups depending on which immune cell leads the attack. In one group, the culprit is T cells—specifically, multiple sclerosis (MS), rheumatoid arthritis (RA), and type 1 diabetes. Here, CD4+ helper T cells spot self-peptides on MHC class II, and CD8+ cytotoxic T cells target peptides on MHC class I. The other group focuses on B cells, with conditions like lupus erythematosus disease (SLE), antiphospholipid syndrome (APS), and IgA nephropathy. These involve autoantibodies homing in on healthy tissues, yet CD4+ T cells still need to assist B cell activation via MHC class II. When it comes to how these attacks start, it hinges on how T cell epitopes are chopped up. Usually, MHC class I shows 8- to 10-mers—perfectly, a 9-residue piece—to CD8+ T cells. On the other hand, MHC class II goes for longer peptides ranging from 12 to 25 residues but sticks with a 9-residue core for CD4+ T cell detection. B cell epitopes differ because they are spotted directly by surface immunoglobulins without MHC restriction. They can be either conformational or linear (Sanchez-Trincado *et al.*, 2017). Our study focuses on molecular mimicry — the concept that microbial peptides mirroring self-antigens might get processed and shown off by MHC molecules, sparking cross-reactive T cells. Given the prevalence and importance of *A. baumanni*, we aimed to determine if infection can lead to susceptibility to and the development of ADs (Rojas *et al.*, 2018). We forecast how well *A. baumannii*-derived similar peptides link up with MHCs. Since MHC binding is crucial for T cell activation and likely autoimmune cross-reactivity, this step is vital (Blum *et al.*, 2013).

2. Materials and Methods

2.1. The identification of peptide similarity

The proteome for *A. baumanni* strain ATCC1906 (proteome ID: UP000005740) was selected from Uniprot (https://www.uniprot.org/proteomes) (Apweiler *et al.*, 2010), and the protein sets were downloaded in FASTA. To find sequences with more than or equal to nine amino acid similarities, the protein sequences of *A. baumannii* were subjected to an NCBI BLASTp (https://blast.ncbi.nlm.nih.gov/Blast.cgi) search (Mahram & Herbordt, 2015) against the *Homo sapiens* proteome. These stretches are potential mimotopes that might, when processed and presented, spark cross-reactive T cell responses. E-value was set to less than or equal to 1e-6 to filter out false positives.

2.2. AD association search of human proteins

To evaluate the possible association of human proteins in the development of ADs, the Gene Autoimmune Disease Association Database (GAAD) (https://gaad.medgenius.info/genes/) (Lu *et al.*, 2018) was employed. GAAD filtered the 5,236 matched human proteins down to those with solid experimental links to ADs. This move let the immunoinformatic analyses focus on peptides connected to the actual autoimmune processes, making the research more targeted. The IDs of the human proteins, obtained from the peptide match search, were provided to the GAAD. The results containing AD names, their aliases, and the number of ADs associated were recorded.

2.3. Prediction of MHCI and MHCII binding affinity of peptides

All peptides with a matching epitope in human AD-associated proteins were subjected to the HLA class I and II binding prediction pipeline. The NetMHCpan-4.1 database (Jurtz *et al.*, 2017) (https://services.healthtech.dtu.dk/services/NetMHCpan-4.1/) was used to find peptides that bind strongly to MHCI. To predict MHCII binding peptides, NetMHCIIpan v.4 databases (Reynisson *et al.* 2020) (https://services.healthtech.dtu.dk/services/NetMHCIIpan-4.2/) were used. These predictions were conducted against 54 different HLAI and 27 HLAII reference alleles. HLA reference sets were extracted from IEDB (Vita *et al.*, 2019) (http://tools.iedb.org/mhci/). The %Rank values for detecting strong bindings (SBs) and weak bindings (WBs) were specified by the corresponding thresholds (%Rank); < 0.5 and < 2 thresholds are considered for detecting SBs and WBs for class I and < 2 and < 10, for SBs and WBs for class II. This helps figure out which peptides our bodies might naturally use to fight infections and could be used in further experiments.

2.4. HLA population coverage

The distribution of HLA in the global population analysis was done using the IEDB (Vita *et al.*, 2019) population coverage tool (http://tools.iedb.org/population/). The studies were performed on HLA classes I and II separately, and the selected areas and populations were set to include all possible areas and populations. The IEDB population coverage tool was used to figure out what proportion of the global population could present each chosen peptide. The analysis looks at HLA allele frequencies across 16 different geographical groups.

2.5. Identification of proteins' subcellular location

Analysis of the cellular location of human and *A. baumanni* proteins containing strong binding peptides and peptides binding to alleles with high population coverage was performed by searching in the Uniprot KB. In the case of proteins with no available location information, online prediction tools of CELLO v.2.5 (Chen *et al.*, 2024) (http://cello.life.nctu.edu.tw), PSORTb v.3.0.3 (Yu *et al.*, 2010) (https://www.psort.org/psortb/), and PLSpred (Bhasin *et al.*, 2005) (https://webs.iiitd.edu.in/raghava/pslpred/) were applied. This step predicted where *A. baumannii* proteins would be in the cell, either inside or outside. Proteins on the cell surface or in the outer membrane can more easily be spotted by the host's immune system. Unlike these, cytoplasmic proteins are pretty hidden during early infections. So, they do not trigger many immune reactions then (Finlay & McFadden, 2006).

3. Results and Discussion

The study includes in-silico analyses of the *A. baumann* strain ATCC1906 proteome to determine the most potent ADs induced by *A. baumanni* peptides. The design of multiple steps aided in gathering predictive data about the ability of the *A. baumanni* proteome to trigger ADs following the infection. The following diagram shows the study procedure to better understand the analyses being performed (Figure 1).

3.1. Candidate peptides identification

Out of 3765 proteins of ATCC 1906 *A. baumannii*, 270 showed sequence similarity with 5236 human proteins. Detailed results for the number of peptide sequences with longer than or equal to 9 amino acids in human proteins are shown in Figure 2.

3.2. Identification of proteins linked to AD and binding potential of candidate peptides to MHC alleles

Using GAAD, it was determined that out of 5236 human proteins, 957 were associated with some AD. From these proteins, 213 unique peptide sequences were identified (i.e., identical peptide matches shared between *A. baumannii* and human AD-associated proteins, with duplicates removed).

These sequences helped predict MHCI and MHCII binding affinities.

Twelve different peptide sequences (Table 1) were predicted to have a strong bond with MHCI alleles, and thirteen different epitopes (Table 2) were predicted to bind strongly with human MHCII alleles.

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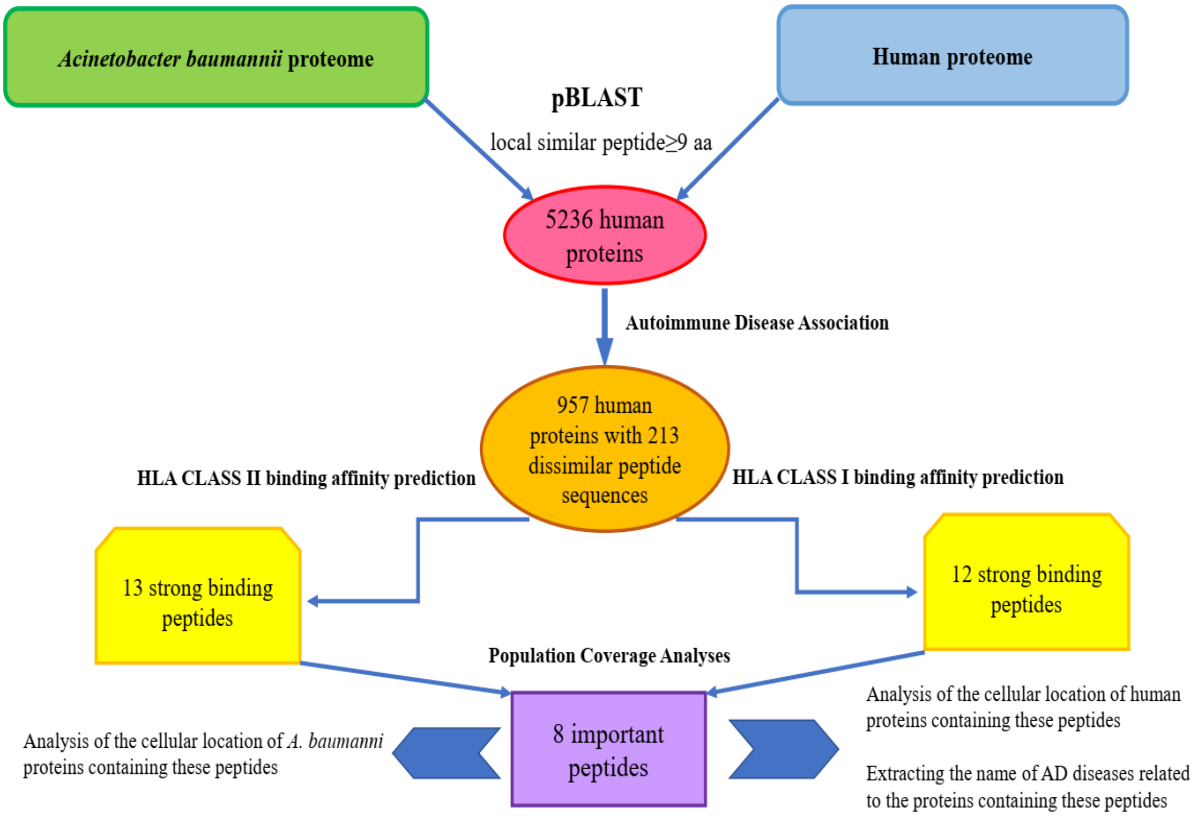

Figure 1. The Study Flowchart

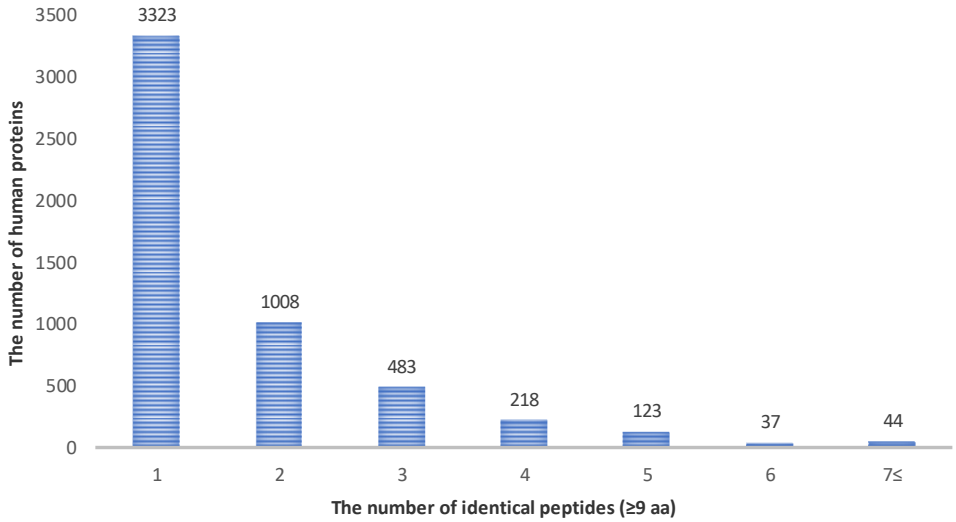

Figure 2. Distribution of human proteins by the number of identical peptide sequences shared with *A. baumannii*. (**Note.** The x-axis shows the number of identical peptide matches (≥9 amino acids) found in a single human protein; the y-axis shows the count of human proteins falling into each category. For example, the first bar represents the number of human proteins that shared exactly one identical peptide with *A. baumannii*, the second bar represents those sharing two identical peptides, and so on.)

Table 1. Predicted Strong MHCI-binding Peptide Sequences from A. baumannii with Identical Matches in Human AD-associated Proteins

Peptide Sequences	MHCI allele	*% Rank	World population coverage percentage
LPGAGGTQRL	HLA-B07:02	0.3199	12.78
AVITVPAYF	HLA-B15:01	0.2289	8.44
	HLA-A26:01	0.1551	5.82
	HLA-A32:01	0.13	4.61
YVGAGTVEF	HLA-B15:01	0.3458	8.44
	HLA-B35:01	0.2313	8.42
GPNTGGMGAY	HLA-B35:01	0.3991	8.42
DTNGAGDAF	HLA-B35:01	0.4493	8.42
	HLA-A26:01	0.18	5.82
CEAHLGHVF	HLA-B40:01	0.1237	7.81
	HLA-B44:02	0.1237	7.61
	HLA-B44:03	0.1211	6.27
AENFPFCTI	HLA-B40:01	0.3172	7.81
	HLA-B44:03	0.3912	6.27
	HLA-B44:02	0.3172	7.61
AHEFGHALGL	HLA-B44:02	0.486	7.61
	HLA-B40:01	0.486	7.81
	HLA-B44:03	0.4034	6.27
DATTNPSLI	HLA-B51:01	0.0844	7.43
SVPAILKGW	HLA-B57:01	0.4374	3.90
	HLA-B58:01	0.4711	3.42
	HLA-A32:01	0.3819	4.61
GAEPLFFLDY	HLA-A01:01	0.3981	17.34
KPVIAAVNGYA	HLA-A30:02	0.4962	2.43

*A lower Rank% indicates a stronger predicted binding affinity. Rank% of 0.5 means the peptide's predicted affinity is better than 99.5% of the peptides in the reference set.

CEAHLGHVF was selected as a key MHCI-binding peptide considering both binding strength (low %Rank) and breadth of HLA coverage — it bound three different HLA-B alleles, the highest among the 12 peptides in Table 1. CEAHLGHVF was picked over DATTNPSLI despite having a higher %Rank (0.1211 versus 0.0844). CEAHLGHVF demonstrated strong binding to three different HLA alleles (B40:01, B44:02, B44:03), whereas DATTNPSLI only attached to one (B51:01). Since CEAHLGHVF caters to more people by attaching to various alleles, it stands out more for practical use than DATTNPSLI, which links better to just one allele. QIQGFFDIPVDN was selected as the key MHCII-binding peptide based on the same criteria used for MHCI: it showed the strongest predicted binding affinity (%Rank = 0.06, the lowest among all 13 MHCII peptides) and bound to two different HLA-DQ alleles (DQA110501/DQB10501 and DQA110301/DQB10302), demonstrating both high affinity and broader HLA coverage. Moreover, among MHCI epitopes, the peptide sequence of YVGAGTVEF (Table 1) was also considered an essential epitope, which is also embedded in the core of the AVNYVGAGTVEFI MHC-II epitope for HLA-DRB109:01(Table 2).

Table 2. Predicted Strong MHC II-binding Peptide Sequences from A. baumannii with Identical Matches in Human AD-associated Proteins

Peptide Sequences	Core peptide	MHCII allele	*% Rank	World population coverage percentage
AALTGLPFVTAPNKFEALA	FVTAPNKFE	DRB1_0405	0.81	3.02
TVPAYFNDAQRQATKDAG	FNDAQRQAT	DRB1_0802	1.6	2.33
	FNDAQRQAT	DRB1_1101	1.39	10.54
	YFNDAQRQA	DRB3_0101	1.07	-**
VKVVILGQDPYHGPNQA	VVILGQDPY	DRB1_1201	0.41	4.47
	ILGQDPYHG	DRB4_0101	0.58	-**
VTLISPFVGRILDW	ISPFVGRIL	DRB1_1501	0.48	18.41
KVLIANRGEIA	LIANRGEIA	DRB3_0202	1.68	-**
QIQGFFDIPVDN	IQGFFDIPV	HLA-DQA10101-DQB10501	0.06	31.46
AIGTGTDVAIEAA	GTGTDVAIE	HLA-DQA10301-DQB10302	1.47	40.19
INEPTAAALAYGL	NEPTAAALA	HLA-DQA10102-DQB10602	0.81	34.55
	PTAAALAYG	HLA-DQA10501-DQB10301	0.21	56.45
VNPDEAVAIGAAIQG	DEAVAIGAA	HLA-DQA10102-DQB10602	0.84	34.55
	DEAVAIGAA	HLA-DQA10301-DQB10302	0.38	40.19
PENEPGSSIMPGKVNPTQ	IMPGKVNPT	HLA-DQA10501-DQB10301	1.7	56.45
AVNYVGAGTVEFI	VGAGTVEFI	HLA-DQA10501-DQB10301	1.07	56.45
	YVGAGTVEF	DRB1_0901	0.88	6.40
	VGAGTVEFI	HLA-DQA10501-DQB10201	1.94	49.64
LGVPFNIASYALLT	FNIASYALL	HLA-DPA10103-DPB10401	1.15	79.22
GASRAAVDAGFVPND	RAAVDAGFV	HLA-DPA10201-DPB11401	0.16	32.81

* A lower Rank% indicates a stronger predicted binding affinity. Rank% of 2 means the peptide's predicted affinity is better than 98% of the peptides in the reference set. ** Population coverage information of this allele is not provided in the Allele Frequency Net Database.

Class I MHC molecules are commonly expressed in nucleated cells and usually present antigens to CD8+ T cells. Furthermore, Class II MHCs are present in dendritic cells, B cells, and macrophages, which present antigens for CD4+ T cells (Axelrod *et al.*, 2019). Cytolytic T cells, which are activated by class I MHC representing APC, can directly attack their target by cell lysis, whereas helper T cells (activated by class II MHC) release cytokines that can either affect targets directly or activate other immune cells, including macrophages, monocytes, and B cells, which in turn respond to target cells (Delogu *et al.*, 2011). Usually, specialized autoantigens are removed in the thymus gland during T cell maturation. However, the proliferation of autoreactive T cells is responsible for AD development. Evidence suggests that autoreactive T cells are produced due to failure in self-tolerance mechanisms; this, coupled with the interactions between MHCs and autoantigenes, leads to the activation of the immune system and, thus, the self-immune response (Thapa & Farber, 2019). Macrophages and dendritic cells are antigen-presenting phagocytic cells that engulf bacteria and other antigenic agents inside phagosomes. This process is followed by proteolytic degradation and antigen presentation through class I and II MHC proteins. Bacteria or viral infections can lead to the development of ADs by host antigen mimicry or by the initiation of a pre-inflammatory environment (Tai *et al.*, 2018). Studies indicate that *A. baumannii* not only can infect several mammalian species but also can infect living cells and reside inside unaffected; this process occurs separately from phagosomic digestion and leads to the initiation of autophagic processes in infected cells. In these cells, autophagy leads to peptide presentation by MHC II and MHC I proteins for their respective targets (Crotzer & Blum, 2009).

3.3. Population Coverage Analyses

Performing the population coverage analyses, the possible world coverage of each MHCI binding peptide (Table 1) and MHCII binding peptides (Table 2) was evaluated. The results indicated that, regarding the peptides binding the alleles with the highest population coverages, the GAEPLFFLDY (world coverage 17.34%) and LPGAGGTQRL (world coverage 12.78%) were the top MHCI binding peptides. As for the MHCII binding peptides, the peptides LGVPFNIASYALLT (world coverage 79.22%), INEPTAAALAYGL, PENEPGSSIMPGKVNPTQ, and AVNYVGAGTVEFI (world coverage 56.45%) were the top peptides. Information on human and bacterial proteins containing these potential AD-inducing peptides is given in Table 3 and is discussed one by one in the following.

CEAHLGHVF epitope was predicted to form the strongest binding to MHCI (% Rank = 0/1211).

Table 3. Characteristics of the Most Important* MHCI and MHCII Binding Peptides

Peptide sequence	Bacterial Protein ID, name and subcellular location	Human Protein name and subcellular location	Associated Autoimmune Disease	Human Gene name
AVNYVGAGT VEFI YVGAGTVEF	D0CG40_ACIB2 Putative acetyl-CoA carboxylase, biotin carboxylase subunit Cytoplasm	3-methylcrotonyl-CoA carboxylase alpha subunit Cytosol and mitochondrial matrix	Parkinson's **disease	MCCC1
CEAHLGHVF	D0C830_ACIB2 Peptide methionine sulfoxide reductase MsrB Cytoplasm	Methionine sulfoxide reductase B2 Cytoplasm, cytosol and mitochondrion	Vitiligo	MSRB2
QIQGFFDIPVD N	D0C9L8_ACIB2 Ribose-phosphate Pyrophosphokinase Cytoplasm	Phosphoribosyl pyrophosphate synthetase 2 Cytoplasm, cytosol	Systemic lupus erythematosus	PRPS2
GAEPLFFLDY	D0CBK1_ACIB2 Phosphoribosylformylglycinamidi ne cyclo-ligase Cytoplasm	trifunctional purine biosynthetic protein adenosine-3 Cytosol, extracellular exosome	Inflammatory bowel disease	GART
LPGAGGTQRL	D0C8K0_ACIB2 Enoyl-CoA hydratase/isomerase family protein Cytoplasm	Trifunctional enzyme subunit alpha Mitochondrion	Rheumatoid arthritis	HADHA
LGVPFNIASY ALLT	D0CAK0_ACIB2 Thymidylate synthase Cytoplasm	Thymidylate synthase Cytoplasm, cytosol, mitochondrion, nucleus	Rheumatoid arthritis Systemic lupus erythematosus	TYMS
INEPTAAALA YGL	D0CBR3_ACIB2 Putative chaperone protein HscC Cytoplasm	Heat shock protein 9 (mortalin) Cytoplasm, extracellular exosome, mitochondrion and nucleus	Multiple sclerosis	HSPA9
PENEPGSSIMP GKVNPTQ	D0C6F4_ACIB2 Fumarate hydratase class II Cytoplasm	Fumarate hydratase Cytoplasm, extracellular exosome, mitochondrion and nucleus	Antiphospholipid syndrome Systemic lupus erythematosus IgA nephropathy Multiple sclerosis Rheumatoid arthritis	FH

* Peptides that bind with high affinity and bind to HLA alleles with high population coverage. **Parkinson's disease is classified as a neurodegenerative disorder; it is included here due to evidence of immune involvement.

This epitope is present in methionine sulfoxide reductase B2, an MSRB2 gene product, and plays a role in preserving mitochondrial integrity by decreasing the intracellular reactive oxygen species build-up (Cabreiro *et al.*, 2008). MSRB2 has been associated with Vitiligo, an AD that causes patches of skin to lose pigment or color (Kaushik *et al.*, 2023). Bacterial protein containing this epitope belongs to the MsrB Met sulfoxide reductase family proteins. In autoimmunity, the immune response directly drives the disease process by impacting protein levels and reducing its function. No scientific literature contains information about a direct relationship between vitiligo and *A. baumannii.* However, the significantly decreased expression/activities of MSRB2 were reported in the epidermis of vitiligo patients (Schallreuter *et al.*, 2008; Taungjaruwinai *et al.*, 2009).

The QIQGFFDIPVDN epitope was predicted to form the strongest bond (%Rank =0.06) with MHC II proteins. Human protein containing this sequence is coded by the PRPS2 gene, which is associated with SLE. Although there are many reports about *A. baumannii* isolation from hospitalized patients with SLE (Lam & Huang, 1997; G. Li *et al.*, 2025; Zhan *et al.*, 2018), this bacterium has not been reported as a causative agent of SLE. Also, some bacterial peptides seem similar to autoantigens linked with SLE (Berkun *et al.*, 2009). Interestingly, the association of genetic variation on PRPS2 to SLE has been detected previously (Zhang *et al.*, 2015).

AVNYVGAGTVEFI MHC II epitope, including YVGAGTVEF MHCI epitope, was also considered an essential epitope due to its binding affinity to MHC I and MHC II proteins. Human protein containing this sequence is coded by the MCCC1 gene, which is associated with Parkinson's disease (PD). Although PD is primarily classified as a neurodegenerative disorder, we included it due to accumulating evidence of T cell-mediated autoimmune mechanisms in its pathogenesis (Garretti *et al.*, 2019). It is worth mentioning that KVLIANRGEIA, one of the strong MHC II binding peptides (Table 2), is also excited in the MCCC1 gene product sequence. Human MCCC1 protein resides inside the mitochondrial matrix of ependymal cells and that of the microglia and oligodendrocytes. MCCC1 gene dysregulation leads to complications in the leucine catabolism pathway, ultimately resulting in acidemia. Bacterial proteins containing these two sequences are biotin carboxylase and acetyl-CoA carboxylase (Chu & Cheng, 2007). PD is the second most common type of neurological disorder. By 2030, the number of individuals suffering from it is expected to show a 50 percent increase (De Virgilio *et al.*,

2016). Studies indicate that T lymphocytes of PD patients can react to microglia with MHC II and to dopaminergic neurons with MHC I by recognizing specific peptide sequences (Garretti *et al.*, 2019). No studies have been made on the possible effect of *A. baumannii* infection on the development of PD. The underlying mechanism by which MCCC1 contributes to the development of PD has not been discovered. However, findings indicate that a mutation in MCCC1 can lead to a higher risk of PD (N. Li *et al.*, 2013; Wang *et al.*, 2014).

GAEPLFFLDY was the peptide binding to HLA-A01:01 with a high population coverage of 17.34%. Human protein containing this sequence is coded by the GART gene, which is associated with Inflammatory bowel disease (IBD). It is a lifelong disorder characterized by chronic gastrointestinal tract inflammation (Ramos & Papadakis, 2019). Alterations in the gut microbiota have been observed in individuals with IBD (J. S. Glover, 2024). *Acinetobacter* species' role in promoting intestinal inflammation has been revealed (J. Glover *et al.*, 2024). The human GART gene encodes a trifunctional enzyme that catalyzes three distinct reactions as part of the 'de novo' inosine monophosphate biosynthetic pathway (Welin *et al.*, 2010). To our knowledge, GART's association with IBD has not yet been detected. Conversely, GART expression is reported to be up-regulated in patients with active colitis and colorectal cancer (Bai *et al.*, 2016).

LPGAGGTQRL was the peptide binding to HLA-B07:02 (world coverage 12.78%). Human protein containing this sequence is coded by the HADHA gene, which is associated with RA. RA is where the immune system attacks the tissue lining the joints (Bullock *et al.*, 2019). This gene encodes a mitochondrial trifunctional enzyme that catalyzes the last three of the four reactions of the mitochondrial beta-oxidation pathway (Liang *et al.*, 2018). Although there are case reports of septic arthritis caused by *A. baumannii* (Duan *et al.*, 2010; Yang *et al.*, 2015), no report has been referred to its association with RA. The noteworthy point is that the down-regulation of HADHA in RA patients has been verified in previous studies (Clayton *et al.*, 2021; Yang *et al.*, 2015).

LGVPFNIASYALLT was the top MHC II binding peptide with regard to allele world coverage (79.22%). Human protein containing this sequence is coded by the TYMS gene, which is associated with RA and SLE. This gene encodes a protein that contributes to the de novo mitochondrial thymidylate biosynthesis pathway for thymidine monophosphate (dTMP) synthesis. The loss of dTMP causes DNA damage and cellular replication loss (Anderson *et al.*, 2011). The role of TYMS polymorphisms on methotrexate (MTX) therapeutic outcomes in RA patients in different populations has been proven (Lima *et al.*, 2014). TYMS is used as a target for several drugs (i.e., MTX for RA treatments) for the downregulation of cell proliferation (Lv *et al.*, 2018; Muralidharan *et al.*, 2017; Senapati *et al.*, 2014). Downregulation of TYMS has not been reported as a causative factor of RA (Wierczeiko *et al.*, 2024). A null association was observed between TYMS polymorphism and SLE risk (Rupasree *et al.*, 2014).

INEPTAAALAYGL and PENEPGSSIMPGKVNPTQ were ranked second in their binding allele, HLA-DQA10501-DQB10301, world population coverage (56.45%). The first peptide is part of the human HSPA9-coded heat shock chaperone protein associated with MS. It is an AD that damages the nerve cells in the brain and spinal cord (Dobson & Giovannoni, 2019). The real-world studies on anti-*Acinetobacter* antibodies mainly exist for MS. Several published studies show that people with MS have way more antibodies against *Acinetobacter* than healthy folks. Plus, there is cross-reactivity between Acinetobacter peptides and both myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG). Because of this, experts suggest a molecular mimicry situation, where an Acinetobacter infection might set off an autoimmune response against central nervous system myelin proteins in certain genetically predisposed individuals (Hughes *et al.*, 2001; Ebringer *et al.*,2012). To date, the protective effects of HSPs in a variety of brain disease models (e.g., Alzheimer's disease, PD, and MS) have been observed (Turturici *et al.*, 2014).

Human protein containing the PENEPGSSIMPGKVNPTQ sequence is coded by the FH gene, which is associated with a variety of ADs, including APS, IgA nephropathy (IgAN), MS, RA, and SLE. FH gene product, fumarate hydratase (FH), catalyzes the reversible stereospecific interconversion of fumarate to L-malate (Ajalla Aleixo, Rangel, Rustiguel, de Pádua, & Nonato, 2019). APS is characterized by antiphospholipid antibodies and blood clots (thrombosis) (Garcia & Erkan, 2018). The search results provided did not contain any direct correlation between APS and *A. baumannii* or FH gene dysregulation. However, an *A. baumannii* infection could increase the risk of complications from blood clots and infection in APS patients (Shakhshir *et al.*, 2024). IgAN is a kidney disease in which IgA deposits build up in the kidneys, causing nephron damage (Coppo & Robert, 2020). While search results on the direct relationship between IgAN and FH are limited, the indirect association is apparent (Sarkar *et al.*, 2022). Hereditary leiomyomatosis and renal cell cancer (HLRCC) are caused by mutations in the FH gene (Kiuru & Launonen, 2004). Individuals with a history of other related kidney diseases might have a higher risk of developing IgAN (Sato *et al.*, 2021). The search results did not highlight a specific direct link between IgAN and *A. baumannii*. The kidney function of IgAN patients can be indirectly worsened by *A. baumannii* (Kadono *et al.*, 2015). It was demonstrated that, in progressive MS, the mesenchymal stromal cells (MSC) secretome has lower levels of mitochondrial FH (Sarkar *et al.*, 2022). As tricarboxylic acid (TCA) cycle metabolites modulate signaling pathways of immune cells by their pro- and anti-inflammatory roles, fumarate could have specific roles in regulating the production of such cytokines and macrophage activation. Therefore, FH loss has been found to lead to DNA and RNA release from mitochondria, sensed by responding proteins. Decreased FH levels have been identified in AD, such as SLE and RA (Peace *et al.*, 2024). Overall, the sum of the results showed possible roles of *A. baumannii* infection in starting serious immune-mediated and ADs, including PD, Vitiligo, IBD, SLE, RA, MS, APS, and IgAN. It is important to note that the number of HLA alleles a peptide binds is not directly proportional to its population coverage. Binding breadth and population coverage are complementary but separate

factors. For example, YVGAGTVEF binds four MHC I alleles but only reaches 8.44% world coverage. On the other hand, GAEPLFFLDY binds three alleles and achieves 17.34% coverage because of the higher global frequency of HLA-A*01:01. MHC II peptides like LGVPFNIASYALLT (with 79.22% coverage) gain high coverage by binding just one common HLA haplotype. Therefore, we viewed both binding affinity and population coverage as complementary factors when prioritizing candidate peptides for further study.

4. Conclusion

This study offers a genome-to-proteome view of the possible connection between *A. baumannii* and AD. These findings identify candidate peptides that may, subject to experimental validation, be relevant to various immune-mediated and autoimmune conditions, including PD, vitiligo, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, antiphospholipid syndrome, and IgA nephropathy. The high-affinity epitopes identified serve as candidate targets for future experimental validation, serological studies, and possibly personalized risk assessment related to HLA haplotypes. Overall, our findings suggest a possible molecular link between an opportunistic pathogen and autoimmunity. This provides a basis for focused follow-up studies, which could reveal new ways to assess risk and implement interventions in ADs. It is important to note that sequence similarity and predicted MHC binding affinity are just the first checkpoints in the molecular mimicry hypothesis. Full autoimmune development requires: (i) proteasomal and endosomal processing of the bacterial protein (Shedlock & Shen, 2003); (ii) the presence of cross-reactive T cells in the host repertoire (Rojas *et al.*, 2018); (iii) an inflammatory context that provides co-stimulatory signals during infection; and (iv) a genetic background that allows for specific HLA haplotypes (Dendrou *et al.*, 2018). Our findings identify candidate mimotopes that meet the first checkpoint of molecular mimicry, showing enough sequence identity and predicted MHC binding to justify experimental evaluation. Experimental validation using infection models, patient sera, or animal models is essential to confirm the immunogenicity and pathogenic potential of the identified peptides. These candidates should undergo testing in functional assays such as peptide-MHC tetramer staining, T cell proliferation assays, cytokine ELISpot using PBMCs from *A. baumannii*-convalescent patients, and antibody cross-reactivity studies (Kern *et al.*, 2005; Rojas *et al.*, 2018). This validation is the next logical step and lies outside the focus of the current in silico study, but our results provide a prioritized framework for those investigations.

Conflict of interest

The authors declare no conflict of interest.

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Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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Authors' Contributions

E. Z. H and G. M designed the study. R. E. J. and E. Z. H. performed bioinformatic analyses. MS. M. wrote the first draft of the manuscript. E. Z. H and G. M edited the manuscript. All authors have read and approved the final version of the manuscript.

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