Triggering type 1 diabetes post-covid: molecular mimicry?

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Short Report

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Abstract

Objective

To evaluate the possible similarity between the AA sequences of human insulin and human glutamic acid decarboxylase-65 (GAD65) with the SARS-CoV-2/COVID proteins to explain the possible trigger of DM1.

Methods

AA sequences of human insulin, GAD65 and SARS-CoV-2 were obtained from the Protein Data Bank archive information database (RCSB PDB). NetMHCpan v4.1 was used for epitope prediction. Sequences were compared using BLAST for epitope comparison and Pairwise Structure Alignment to assess protein similarity. The AA sequences of human insulin (4F0N) and GAD65 (2OKK) were compared with the sequences of the following SARS-CoV-2 proteins: SARS-Cov2 S protein at open state (7DDN), SARS-Cov2 S protein at close state (7DDD), SARS CoV-2 Spike protein (6ZB5), Crystal structure of SARS-CoV-2 nucleocapsid protein N-terminal RNA binding domain (6M3M), Crystal structure of SARS-CoV-2 nucleocapsid protein C-terminal RNA binding domain (7DE1), Crystal structure of NSP1 from SARS-CoV-2 (7K3N), and SARS-CoV-2 S trimer (7DK3)).

Results

The percent similarity between epitopes ranged from 45 to 60% (P 0.048) between both human insulin and SARS-CoV2 and for GAD 65 and SARS-CoV2, while the AA similarity of the evaluated samples ranged from 5.00–45.45% between human insulin and SARS-CoV2 and from 10.45–22.22% between GAD65 and SARS-CoV2.

Conclusion

Immunoinformatics data suggest a potential pathogenic link between SARS-CoV-2/COVID and DM1. Thus, by molecular mimicry, we found that sequence similarity between epitopes and AA sequence between SARS-CoV-2 / COVID and human insulin and GAD65 could lead to the production of an immune cross-response to self-antigens, with self-tolerance breakdown, which could thus trigger DM1.

Introduction

Coronavirus disease (COVID-19) and diabetes mellitus (DM) are two pandemics with high impact on public health worldwide.

Coronaviruses (CoV) are enveloped, positive single-stranded RNA viruses, widely dispersed in animals and humans worldwide, and responsible for causing respiratory infections in humans, notably severe

acute respiratory syndrome (SARS).[1] CoV is formed from the following structural proteins: spicule (S), membrane (M), nucleocapsid (N), and envelope (E). CoV after its entry into the host cell through the intrinsic action of the cell receptor and the viral envelope glycoprotein spicule (S), replicates in the cytoplasm in the same way as other positive single-stranded RNA viruses.[2] Human CoV can lead to potential complications such as SARS-CoV-2, also called COVID-19.[3]

Type 1 diabetes (T1DM) occurs due to an imbalance between Th1 and Th2 immunity resulting in insulitis and destruction of pancreatic beta cells (β-cells) and consequent reduced or absent insulin production.[4] Several factors encompassing genetic factors, environmental factors, and multiple viral infections may contribute to the development of T1DM.

A recent observational cohort study of DM1 pathogenesis monitored clinical infections and pancreatic islet autoantibodies, assessing the association between respiratory infections with islet autoimmunity, and CoV was identified as one of the viruses present in the study.[5]

β-cells can be destroyed by viral antigens, and possibly SARS-CoV-2 can bind to angiotensin-converting enzyme 2 in the pancreas, particularly in COVID-19 with clinical complications, leading to the triggering of DM1 in susceptible individuals.[6,7] Thus, it is likely that an increase in the incidence of DM1 is triggered by COVID-19 through the production of antibodies against β-cells by cross-reaction with SARS-CoV-2.

Most patients with DM1 develop cellular immune responses to autoantigens to glutamic acid decarboxylase 65 (GAD_{65}), proinsulin, insulin, and a to tyrosine phosphatase.[8]

Theoretically, molecular mimicry would present the possibility in which similarities between foreign peptide sequence and autopeptides trigger a cross-reaction activating T or B lymphocytes developing autoimmune diseases. Thus, the aim of the present study was to evaluate the possible similarity between the epitopes of human insulin and GAD_{65} with the epitopes of SARS-CoV-2 / COVID, in addition to evaluating the possible similarities of the amino acid (AA) sequences of human insulin and GAD_{65} with the AA sequences of SARS-CoV-2 / COVID proteins, to explain the possible triggering of DM1 through molecular mimicry.

Methodology

In the present study, we evaluated the similarities between the epitopes of human insulin and GAD65 with the epitopes of SARS-CoV-2 / COVID, and the similarities of the amino acid (AA) sequences of human insulin and GAD65 with the AA sequences of SARS-CoV-2 / COVID proteins.

The biological structures of GAD_{65}, human insulin and nucleotides of SARS-CoV-2 were obtained from the Protein Data Bank archive information database (RCSB PDB) (https://www.rcsb.org/).

We performed the immunoinformatic prediction of epitopes of insulin, GAD65 and SARS-CoV-2 using NetMHCpan v4.1 software (https://services.healthtech.dtu.dk/service.php?NetMHCpan-4.1), based on

artificial neural networks, following the recommended methodology and filtering the high affinity epitopes based on an IC50 ≤ 50 nM and percentage rank ≤ 0.20 for the respective alleles analyzed, and subsequently performed the comparison of the epitopes to verify the hypothesis of cross-recognition. The similarity analyses were complemented with Parwise an extension of the Protein Data Bank program.

NetMHCpan 4.1 is a server that uses artificial neural networks to filter high affinity epitopes.[9]

We selected the predicted epitopes for the following sequences available in the RCSB PDB: GAD_{65} (2OKK), human insulin (4F0N), and SARS-CoV-2 (SARS-Cov2 S protein at open state (7DDN), SARS-Cov2 S protein at close state (7DDD), SARS CoV-2 Spike protein (6ZB5), Crystal structure of SARS-CoV-2 nucleocapsid protein N-terminal RNA binding domain (6M3M), Crystal structure of SARS-CoV-2 nucleocapsid protein C-terminal RNA binding domain (7DE1), Crystal structure of NSP1 from SARS-CoV-2 (7K3N), and SARS-CoV-2 S trimer (7dk3)). For epitope extraction through NetMHCpan 4.1 we used the FASTA format obtained from the National Center for Biotechnology Information (NCBI) protein database, selected 11mer peptides and the human HLA-A*01:01 allele.

For comparison of epitope candidates we used those with the strongest binding, programmed in NetMHCpan 4.1 between 0.5 and 2.0. The similarity between the sequences of the epitopes of GAD_{65}, human insulin and the epitopes of SARS-Cov2 was the evaluated with the BLAST tool from NCBI.

Pairwise structure alignment is an application to evaluate the similarity between two proteins in homology search,[10] was used as a complementary tool in the evaluation of the homology and similarity between the study proteins on the RCSB PDB website.

The following sequences available in the RCSB PDB were used to assess the similarity between the proteins: GAD_{65} (2OKK), human insulin (4F0N), and the following SARS-CoV-2: SARS-Cov2 S protein in open state (7DDN), SARS-Cov2 S protein in closed state (7DDD), SARS CoV-2 Spike protein (6ZB5), crystal structure of SARS-CoV-2 protein nucleocapsid N-terminal RNA binding domain (6M3M), Crystal structure of the C-terminal nucleocapsid protein of the SARS-CoV-2 RNA binding domain (7DE1), Crystal structure of the NSP1 of SARS-CoV-2 (7K3N), and SARS-CoV-2 S trimer (7dk3).

Results

The prediction of epitopes for GAD65 (2OKK) was found to be 11 candidate epitopes, with three of them having threshold for stronger binding peptides (WB: 0.693-1.302) (Table 1).

For epitope prediction for human insulin (4F0N), 20 candidate epitopes were found, with two epitopes with threshold for stronger binding peptides (WB: 1.153-1.892) (Table 2).

Prediction of epitopes for the SARS-Cov2 S protein at open state (7DDN), 28 candidate epitopes were found, with two of them (SB) having threshold for peptide binding with highly strong (SB: 0.116 and 0.142) (Table 3).

For the prediction of epitopes for the SARS-Cov2 S protein at close state (7DDD), 33 candidate epitopes were found, with four having threshold for high binding power peptides (SB: 0.044 - 0.178) (Table 4).

Prediction of epitopes for the SARS CoV-2 Spike protein (6ZB5), 32 candidate epitopes were found, with three having a threshold for highly strongly binding peptides (SB: 0.116 - 0.178) (Table 5).

No epitopes were found, within the binding pattern established in the software used, for the Crystal structure of SARS-CoV-2 nucleocapsid protein N-terminal RNA binding domain (6M3M) and for the Crystal structure of SARS-CoV-2 nucleocapsid protein C-terminal RNA binding domain (7DE1).

For epitope prediction for the Crystal Structure of NSP1 from SARS-CoV-2 (7K3N), 29 candidate epitopes were found, with five having thresholds for highly strong binding peptides (SB: 0.015 and 0.096) (Table 6).

Prediction of epitopes for the SARS-CoV-2 S trimer (7dk3), 18 candidate epitopes were found, with three having thresholds for highly strongly binding peptides (SB: 0.044 and 0.142) (Table 7).

Similarity analyses between the GAD_{65} epitope and the SARS-CoV-2 epitopes

The percent similarity between the strongest binding GAD_{65} epitope and the SARS-Cov2 epitopes are presented in Table 8.

Table 8. *Similarity between the GAD_{65} epitope and the SARS-Cov2 epitopes.*

GAD_{65} EPITOPE (2OKK)	% SIMILARITY	E-VALUE
7DDN EPITOPE	45-60	0.048
7DDD EPITOPE	45-60	0.048
6ZB5 EPITOPE	45-60	0.048
6M3M EPITOPE	-	-
7DE1 EPITOPE	-	-
7K3N EPITOPE		NON-SIGNIFICANT
7dk3 EPITOPE	45-60	0.048

Similarity analyses between the human insulin epitope and the SARS-CoV-2 epitopes

The percent similarity between the strongest binding human insulin epitope and the SARS-Cov2 epitopes are presented in Table 9.

Table 9. *Similarity between the Insulin epitope and the SARS-Cov2 epitopes.*

INSULIN EPITOPE (KF0N)	% SIMILARITY	E-VALUE
7DDN EPITOPE	45-60	0.048
7DDD EPITOPE	45-60	0.048
6ZB5 EPITOPE		NON-SIGNIFICANT
6M3M EPITOPE	-	-
7DE1 EPITOPE	-	-
7K3N EPITOPE		NON-SIGNIFICANT
7dk3 EPITOPE		NON-SIGNIFICANT

Sequence identity percentages (SI%) and sequence similarity percentages (SS%) were found between 4F0N, 2OKK and SARS-CoV-2.

Amino acid sequence similarity analyses between human insulin and SARS-CoV-2

The similarity between 4F0N and SARS-CoV-2 ranged from 18.75% to 21.74%, distributed thus:

- 4F0N and 7DDN = SI% 4.76 and SS% 28.57 (Figure 1)
- 4F0N and 7DDD = SI% 14.39 and SS% 23.81 (Figure 2).
- 4F0N and 6ZB5 = SI% 4.76 and SS% 28.57 (Figure 3).
- 4F0N and 6M3M = SI% 5.00 and SS% 5.00 (Figure 4).
- 4F0N and 7DE1 = SI% 4.76 and SS% 9.21 (Figure 5).
- 4F0N and 7K3N = SI% 9.09 and SS% 45.45 (Figure 6).
- 4F0N and 7DK3 = SI% 4.76 and SS% 28.57 (Figure 7).

Amino acid sequence similarity analysis between GAD_{65} and SARS-CoV-2

The similarity between 2OKK and SARS-CoV-2 ranged from 10.45% to 22.22%, distributed thus:

- 2OKK and 7DDN = SI% 6.70 and SS% 15.64 (Figure 8).
- 2OKK and 7DDD = SI% 7.53 and SS% 18.84 (Figure 9).
- 2OKK and 6ZB5 = SI% 6.68 and SS% 17.38 (Figure 10).

- 2OKK and 6M3M = SI% 4.48 and SS% 10.45 (Figure 11).
- 2OKK and 7DE1 = SI% 6.67 and SS% 22.22 (Figure 12).
- 2OKK and 7K3N = SI% 3.19 and SS% 15.97 (Figure 13).
- 2OKK and 7DK3 = SI% 3.95 and 17.98 (Figure 14).

Discussion

Although SARS-CoV-2 is not yet listed among the viruses involved in the etiology of DM1, our study proposed to evaluate the triggering of DM1 by molecular mimicry through protein similarity. Our results, using immuno-informatics tools, in assessing the similarity between the epitopes and the AA sequence of GAD_{65}, human insulin and 7 select proteins of SARS CoV-2, can substantiate that DM1 induction can be triggered by the 7DDN, 7DDD and 7dk3 proteins of SARS-CoV-2.

The basis of the pathogenesis of DM1 is founded on two pillars: genetic predisposition and the existence of anti-β-cell, anti-GAD_{65}, anti-insulin, and anti-tyrosine phosphatase autoantibodies.[11]

It is possible that SARS-CoV-2 has the ability to lead to pleiotropic modifications in glucose metabolism, complicating existing diabetes or triggering it.[12] There are several reports of a viral etiology of DM1, including coronaviruses that relate to angiotensin-converting enzyme 2 (ACE2) receptors, and it has been observed that a higher incidence of hyperglycemia and DM1 have been reported among patients with SARS-CoV pneumonia than among those with pneumonia of another etiology.[13] Our analyses may support the hypothesis of molecular mimicry as a potential diabetogenic effect of SARS-CoV-2 for triggering DM1.

The term molecular mimicry was first used in 1964 by Damian to describe the expression of similarity between antigens expressed by microorganisms and their human hosts and the immune response.[14] Molecular mimicry is an evolving concept, involving not only similarity between the molecular structure of the microorganism's protein and the human proteome, as well as environmental and genetic factors, and mechanisms concomitant to positive / negative selection of T cells.[15]

The following criteria may be related to molecular mimicry: "similarity between a host epitope and an epitope of a microorganism or environmental agent," "epidemiological link between exposure to the environmental agent or microorganism and the development of autoimmune disease," "reproducibility of autoimmunity in an animal model after sensitization with the appropriate epitopes after infection with the microorganism or exposure to the environmental agent," and "detection of antibodies or T cells that cross-react with both epitopes in patients with autoimmune disease."[16] In our study, we attributed the triggering of SARS-CoV-2-related DM1 to the similarity between the epitopes and the molecular structure of human insulin and GAD65 with the molecular structure of the SARS-CoV-2 protein.

Studies have suggested that molecular mimicry plays an important role in generating autoimmunity in patients with COVID-19.[17,18] To trigger autoimmunity secondary to infection, only 5 to 6 identical AA

between a viral protein and a host protein are required to induce an immune response.[19] In this work, we analyzed the similarity between the epitopes of 7 SARS-CoV-2 polyprotein sequences and 2 specific human beta cell protein antigens, and observed that SARS-CoV-2, human insulin, and GAD65 share AA sequence similarity, and that some regions contain epitopes of SARS-CoV-2 andβ-cell autoantigens with high similarities. We did not find any study in the literature that evaluated the similarity we propose in our study.

GAD_{65} is a neuroendocrine enzyme and is a key autoantigen for triggering DM1, and anti-GAD_{65} autoantibodies are positive in the serum of 70–80% of DM1 patients, and is therefore an important marker in the prediction and diagnosis of DM1.[20] The high-resolution crystal structure of GAD_{65} was created in 2007, thus making available various insights into the molecular determinants of antigenicity, as well as an atomic positioning of epitope mapping data.[21] GAD65 was employed as a function of the various information on molecular determinants of antigenicity triggering DM1. In our study, GAD_{65} showed a higher similarity to the SARS-CoV-2 proteins 7DDN, 7DDD and 7dk3, while the similarity to the other proteins evaluated was not significant, thus supporting the hypothesis that a molecular mimicry could occur between GAD_{65} and SARS-CoV-2.

Insulin is secreted by β-cells, which are indispensable for the body's glycemic homeostasis. In the individual with DM1, an autoimmune insulinitis occurs resulting in the destruction of the β-cells and consequent lack of insulin secretion. Proposed pathogenic mechanisms for DM1 include molecular mimicry, non-autoimmuneβ-cell infection, alterations in thymic T cells, and immune activation.[22] Thus, there is evidence that viral infection in genetically predisposed individuals can activate the immune system through molecular mimicry, triggering DM1. In our study, human insulin showed high similarity to SARS-CoV-2 proteins 7DDN and 7DDD, coinciding with GAD_{65} already described above and also supporting the possible molecular mimicry between human insulin and SARS-CoV-2.

Conclusion

Immunoinformatics data suggest a potential pathogenic link between SARS-CoV-2/COVID and DM1. Thus, by molecular mimicry, we found that sequence similarity between the epitopes and the AA sequence between SARS-CoV-2 / COVID and human insulin and GAD_{65} could lead to the production of an immune cross-response to self-antigens, with self-tolerance breakdown, which could thus trigger DM1.

References

1. Adachi S, Koma T, Doi N, Nomaguchi M, Adachi A. Commentary: Origin and evolution of pathogenic coronaviruses. Front Immunol. 2020;11:811.
2. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020; 181(2):281–292.e6.

3. World Health Organization. Weekly epidemiological update on COVID-19–4 May 2022. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19—4-july-2022.
4. Tatti P, Tonolo G, Zanfardino A, Iafusco D. Is it fair that patients with Type 1 Diabetes (autoimmune) may be spared by the infection of Covid-19. Medical Hypothesis. 2020;14:109795.
5. TEDDY Study Group. The Environmental Determinants of Diabetes in the Young (TEDDY) study: study design. Pediatr Diabetes. 2007; 8:286–98.
6. Op de Beeck A, Eizirik DL. Viral infections in type 1 diabetes mellitus–why the β cells? Nat Rev Endocrinol. 2016;12:263–73.
7. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 expression in pancreas may cause pancreatic damage after SARS-CoV-2 infection. Clin Gastroenterol Hepatol. 2020;18(9):2128–2130.e2.
8. Schloot NC, Willemen SJ, Duinkerken G, Drijfhout JW, de Vries RR, Roep BO. Molecular mimicry in type 1 diabetes mellitus revisited: T-cell clones to GAD65 peptides with sequence homology to Coxsackie or proinsulin peptides do not crossreact with homologous counterpart. Hum Immunol. 2001;62(4):299–309).
9. Jurtz V, Paul S, Andreatta M, Marcatili P, Peters B, Nielsen M. NetMHCpan-4.0: improved peptide-MHC class I interaction predictions integrating eluted ligand and peptide binding affinity data. J Immunol 2017; 199:3360–8.
10. Shindyalov IN, Bourne PE. Protein structure alignment by incremental combinatorial extension (CE) of the optimal path. Protein Eng. 1998; 11(9):739–47.
11. Merger SR, Leslie RD, Boehm BO. The broad clinical phenotype of Type 1 diabetes at presentation. Diabet Med. 2013;30:170–8.
12. Rubino F, Amiel SA, Zimmet P, Alberti G, Bornstein S, Eckel RH, et al. New-Onset Diabetes in Covid-19. N Engl J Med. 2020;383(8):789–90.
13. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010; 47(3):193–9.
14. RT Damian. Molecular mimicry: antigen sharing by parasite and host and its consequences.Am Nat. 1964; 98:129–149.
15. Kirschner M. Systems Medicine: Sketching the Landscape. Methods Mol Biol. 2016;1386:3–15.
16. LK Peterson, RS Fujijami. Molecular mimicry. ME Shoenfeld, ME Gershwin (Eds.), Autoantibodies, Elsevier, Burlington (2007).
17. Cappello F. Is COVID-19 a proteiform disease inducing also molecular mimicry phenomena? Cell Stress Chaperones. 2020;25:381–82.
18. Cappello F, Gammazza AM, Dieli F, de Macario, Macario AJ. Does SARS-CoV-2 Trigger Stress-InducedAutoimmunity by Molecular Mimicry? A Hypothesis. J Clin Med. 2020; 9:2038.
19. Oldstone MB. Molecular mimicry and immune-mediated diseases. FASEB J. 1998;12:1255–65.

20. Jayakrishnan B, Hoke DE, Langendorf CG, Buckle AM, Rowley MJ. An analysis of the cross-reactivity of autoantibodies to GAD65 and GAD67 in diabetes. PLoS One. 2011;6(4):e18411.
21. Atkinson MA, Bowman MA, Campbell L, Darrow BL, Kaufman DL, Maclaren NK. Cellular immunity to a determinant common to glutamate decarboxylase and coxsackie vírus in insulin-dependent diabetes. J Clin Invest. 1994;94:2125–9.
22. Coppieters KT, Wiberg A, von Herrath MG. Viral infections and molecular mimicry in type 1 diabetes. APMIS. 2012;120(12):941–9.

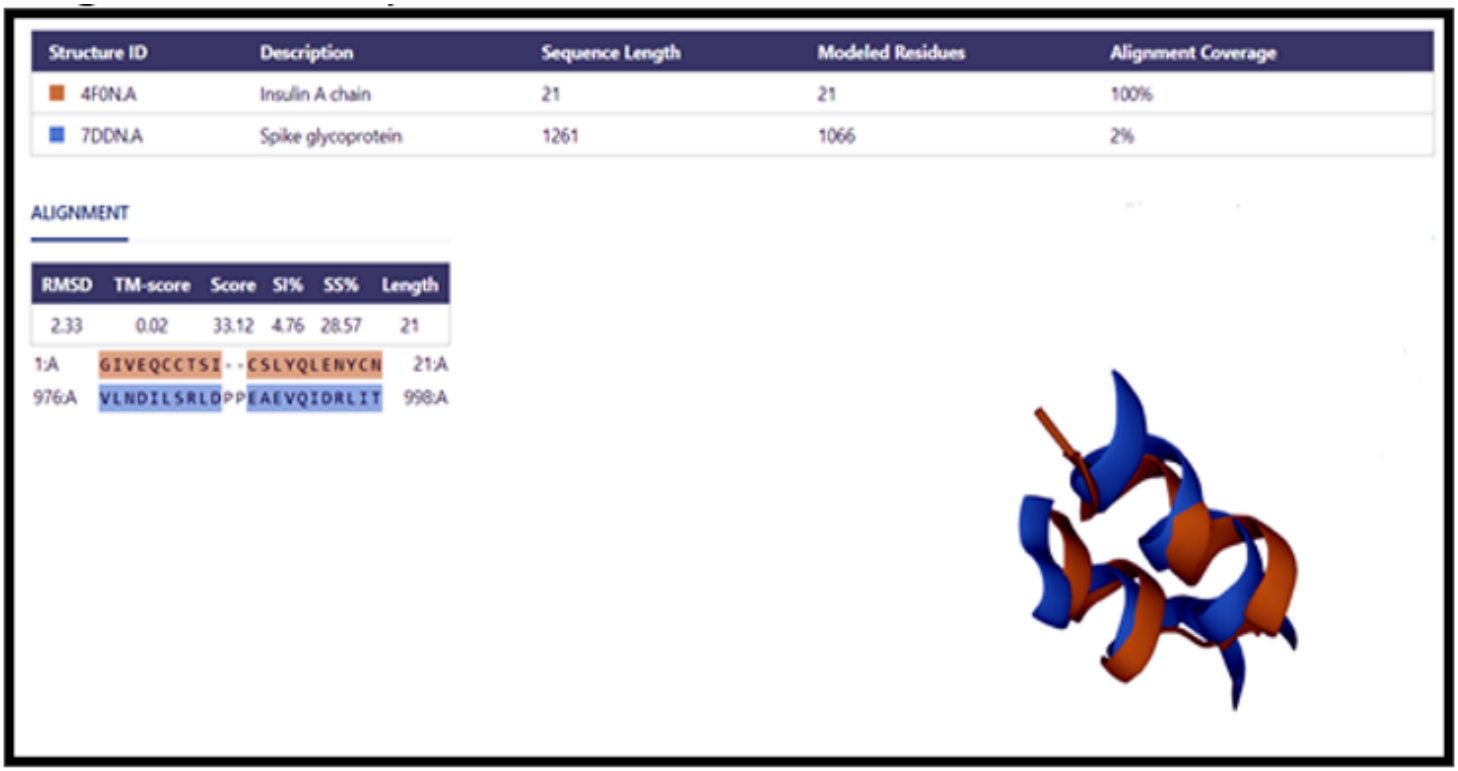
Declarations

Competing interests: The authors declare no competing interests.

Tables

Tables 1-7 are available in the supplementary files section.

Figures



Source: Research result.

Figure 1

Similarity between 4F0N and 7DDN.

Structure ID	Description	Sequence Length	Modeled Residues	Alignment Coverage
4F0N.A	Insulin A chain	21	21	100%
7DDD.A	Spike glycoprotein	1261	1088	2%

ALIGNMENT

RMSD	TM-score	Score	SI%	SS%	Length
2.98	0.02	33.34	14.29	23.81	21

1:A GIVEQCCTSIC--SLYQLENYCN 21:A

835:A KQYGDCLGDIAARDLICAQKFNG 857:A

Source: Research result.

Figure 2

Similarity between 4F0N and 7DDD.

Structure ID	Description	Sequence Length	Modeled Residues	Alignment Coverage
4F0N.A	Insulin A chain	21	21	100%
6ZB5.A	Spike glycoprotein	1259	1032	2%

ALIGNMENT

RMSD	TM-score	Score	SI%	SS%	Length
2.23	0.02	34.35	4.76	28.57	21

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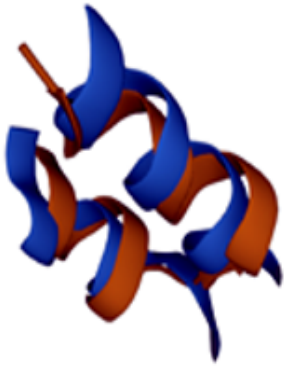
976:A VLNDILSRLDKVEAEVQIDRLIT 998:A



Source: Research result.

Figure 3

Similarity between 4F0N and 6ZB5.

Source: Research result.

Figure 4

Similarity between 4F0N and 6M3M.

Structure ID	Description	Sequence Length	Modeled Residues	Alignment Coverage
4F0N.A	Insulin A chain	21	21	100%
7DE1.A	Oxysterol-binding protein-related protein 3	388	376	6%

ALIGNMENT

RMSD	TM-score	Score	SI%	SS%	Length
2.32	0.05	27.89	4.76	9.52	21

1:A GIVEQCCTSICS--LYQLENYCN 21:A

314:A PDQRFLEEGNLEEAEIQKQRIEQ 336:A

Source: Research result.

Figure 5

Similarity between 4F0N and 7DE1.

Structure ID	Description	Sequence Length	Modeled Residues	Alignment Coverage
4F0N.A	Insulin A chain	21	21	52%
7K3N.A	Host translation inhibitor nsp1	180	106	10%

ALIGNMENT

RMSD	TM-score	Score	SI%	SS%	Length
1.49	0.09	23.28	9.09	45.45	11

11:A CSLYQLENYCN 21:A

33:A DSVEEVLSEAR 43:A

Source: Research result.

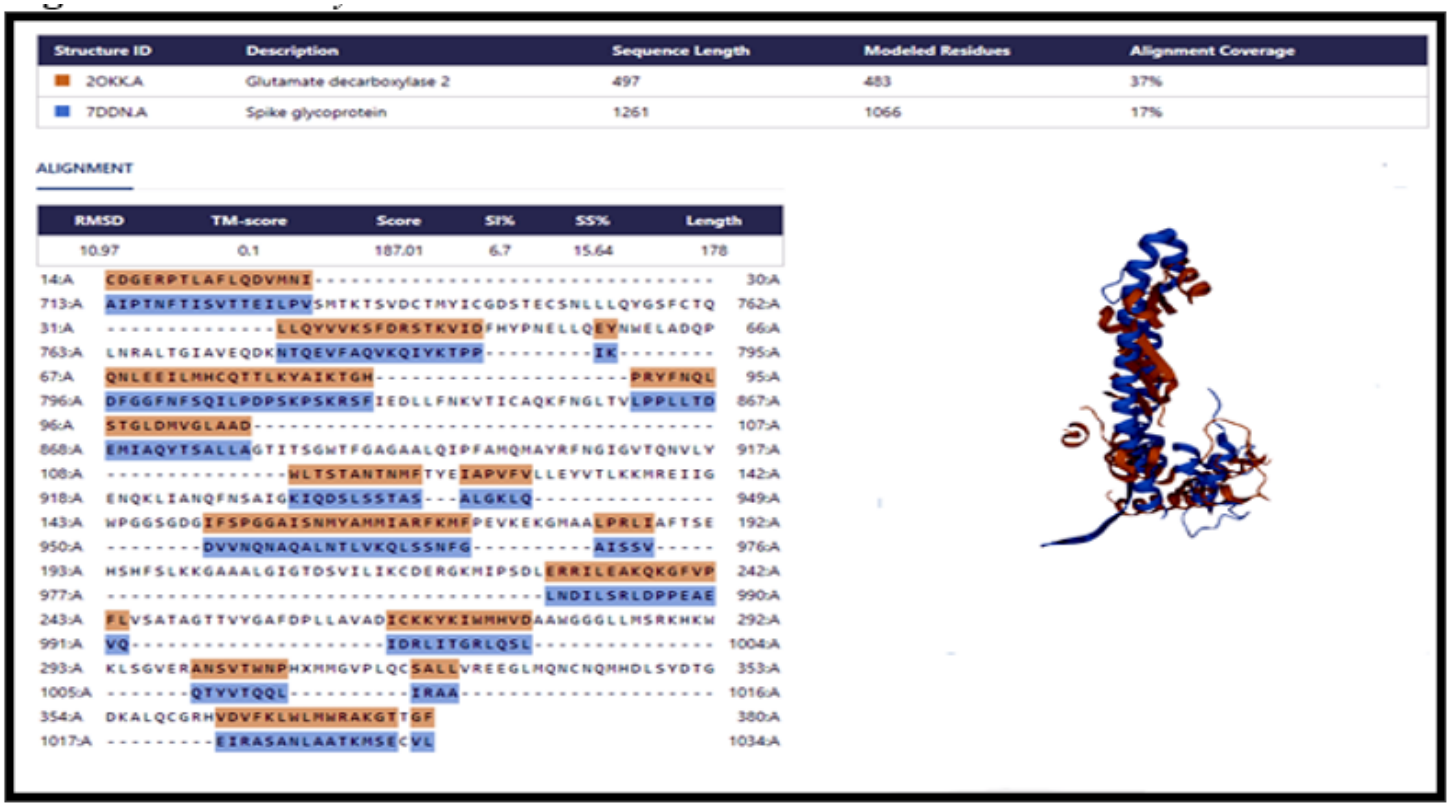
Figure 6

Similarity between4F0N e o 7K3N.

Source: Research result.

Figure 7

Similarity between 4F0N and 7DK3.



Source: Research result.

Figure 8

Similarity between 2OKK e 7DDN.

Source: Research result.

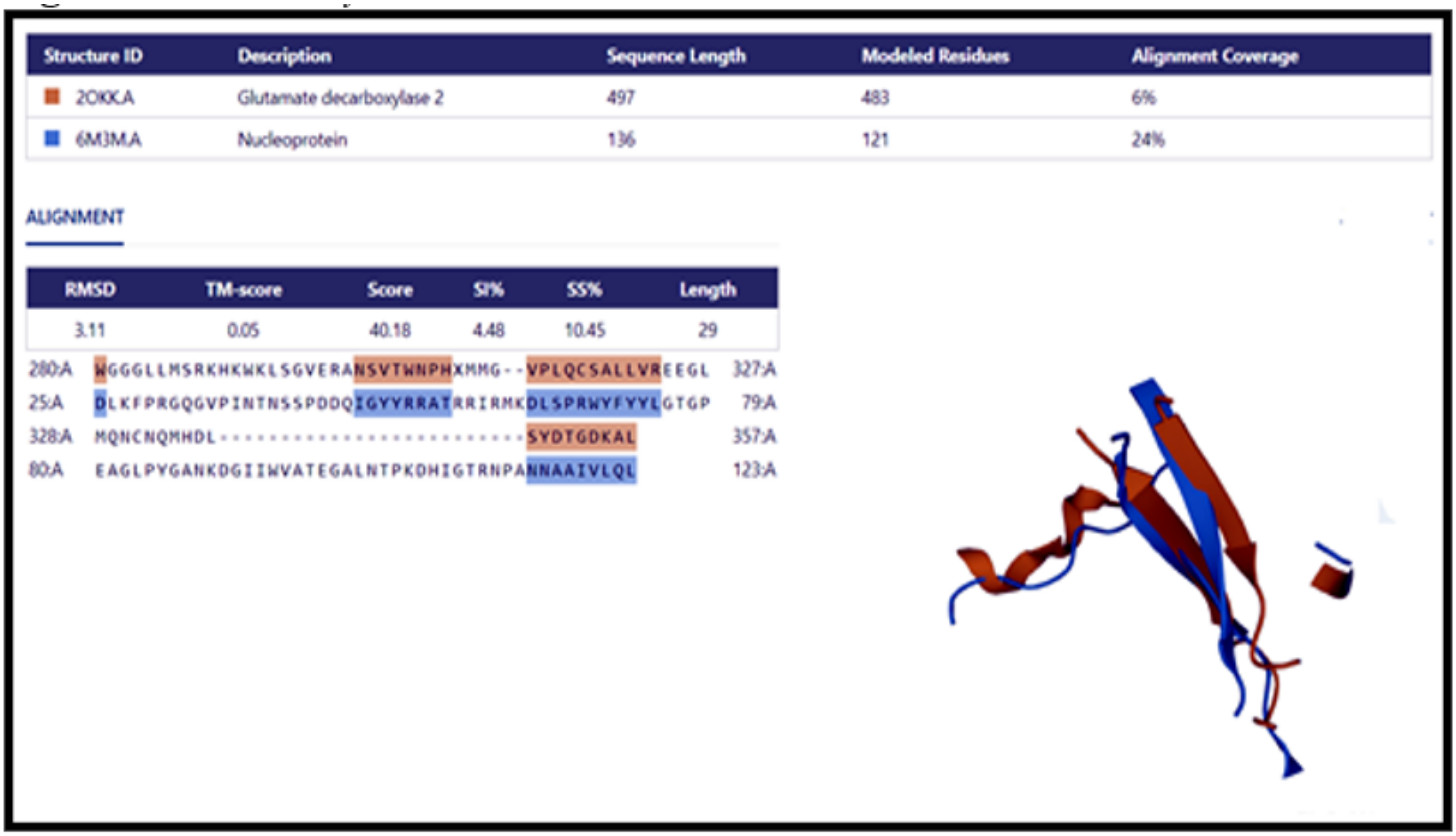
Figure 9

Similarity between 2OKK and 7DDD.

Source: Research result.

Figure 10

Similarity between 2OKK e 6ZB5.



Source: Research result.

Figure 11

Similarity between 2OKK e 6M3M.

Source: Research result.

Figure 12

Similarity between 2OKK and 7DE1.

Source: Research result.

Figure 13

Similarity between 2OKK and 7K3N.

Source: Research result.

Figure 14

Similarity between 2OKK and 7DK3.

Supplementary Files

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