BRIEF REPORT
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Structural similarity between thyroid peroxidase [Homo sapiens] and SARS-CoV-2 spike glycoprotein – An autoimmune thyroiditis triggering mechanism in COVID-19 carriers?

Similaridade estrutural entre a tireoperoxidase humana [Homo sapiens] e a glicoproteína de superfície do SARS-CoV-2 – Um mecanismo de desencadeamento da tiroidite autoimune nos portadores da COVID-19?

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Abstract

Introduction*: there are reports of autoimmune disease related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) such neurological syndromes and hematological syndromes, and more recently autoimmune thyroid dysfunctions have been described. These reports suggest that SARS-CoV-2 acts as a probable trigger for triggering the autoimmunity process.* ***Aim****: to evaluate structural similarity between thyroid peroxidase [Homo sapiens] (TPO) and SARS-CoV-2 spike glycoprotein (COVID-19), and to propose this similarity as a likely trigger for autoimmune thyroiditis.* ***Methodology****: using bioinformatics tools, we compare the amino acids (AA) sequences between protein structure of TPO and chain A COVID-19, chain B COVID-19, and chain C COVID-19, accessible in the National Center for Biotechnology Information database, by Basic Local Alignment Search Tool in order to locate the homologous regions between the sequences of AA.* ***Results****: the homology sequence between the TPO and COVID-19 ranged from 27.0 % (10 identical residues out of 37 AA in the sequence) to 56.0% (5 identical residues out of 9 AA in the sequence). The similar alignments demonstrated relatively high E values in function of short alignment.* ***Conclusion****: data suggest a possible pathological link between TPO and COVID-19. The structural similarity of AA sequences between TPO and COVID-19 may present a molecular mimicry suggesting the possibility of antigen crossover between TPO and COVID-19 that might represent an immunological basis for autoimmune thyroiditis associated with COVID-19.*

Keywords*: Autoimmune thyroiditis. Thyroid peroxidase. SARS-CoV-2. Molecular mimicry.*

Resumo

Introdução: há relatos de doenças autoimunes relacionadas à síndrome respiratória aguda grave por coronavírus 2 (SARS-CoV-2), tais como síndromes neurológicas e hematológicas, e mais recentemente disfunções autoimunes da tireoide foram descritas. Esses relatos sugerem que o SARS-CoV-2 atue como um provável gatilho para desencadear o processo de autoimunidade. **Objetivo**: avaliar a similaridade estrutural entre a peroxidase tireoidiana [Homo sapiens] (TPO) e a glicoproteína de superfície SARS-CoV-2 (COVID-19) e propor essa similaridade como provável gatilho para o desencadeamento da tireoidite autoimune. **Metodologia**: utilizando ferramentas de bioinformática, comparamos as sequências de aminoácidos (AA) entre a estrutura da TPO e a estrutura da cadeia A do COVID-19, a cadeia B do COVID-19 e a cadeia C do COVID-19, acessível no banco de dados do National Center for Biotechnology Information, através da Ferramenta Básica de Pesquisa de Alinhamento Local para localizar as regiões homólogas entre as sequências de AA. **Resultados**: a sequência de homologia entre o TPO e COVID-19 variou de 27,0% (10 resíduos idênticos em 37 AA nas sequências) a 56,0% (5 resíduos idênticos em 9 AA nas sequências). Os alinhamentos semelhantes demonstraram valores E relativamente altos em função do alinhamento curto. **Conclusão**: os dados sugerem uma possível ligação patológica entre TPO e COVID-19. A similaridade estrutural das sequências de AA entre TPO e COVID-19 pode apresentar um mimetismo molecular sugerindo a possibilidade de cruzamento de antígeno entre TPO e COVID-19 que podem representar uma base imunológica para tireoidite autoimune associada a COVID-19.

Palavras-chave: Tireoidite autoimune. Peroxidase tireoidiana. SARS-CoV-2. Mimetismo molecular.

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INTRODUCTION

There are reports of autoimmune disease related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein (COVID-19) such neurological syndromes and hematological syndromes, and more recently autoimmune thyroid dysfunctions have been described. These reports suggest that SARS-CoV-2 acts as a probable trigger for triggering the autoimmunity process[1]. The thyroid hormones are fundamental in regulation of innate immune response[2]. Meanwhile, the component of immunological system in charge for autoimmune thyroid disease is independent to the immunological system responsible for defense of viral infections[3].

The thyroid peroxidase (TPO) has a key role in the functional performance of the thyroid, being an important autoantigen in autoimmune thyroid diseases[4]. Homology models of TPO can be constructed facilitating the mapping of regions responsible for its autoantigenicity.

Coronaviruses is part of the family Coronaviradae, order Nidovirales, with four main genera: Alphacoronaviruses, Betacoronaviruses, Gammacoronaviruses, and Deltacoronaviruses. SARS-CoV-2 is a betacoronavirus which has a spherical shape with spicules on the surface. SARS-CoV-2 has a high sequence identity with bat SARS coronavirus[5]. SARS-CoV-2 infects type II pneumocytes, resulting in significant alveolar damage after infection (6). SARS-CoV-2 uses the spike protein to penetrate the host cells by binding the inlet receptor of the angiotensin 2 converting enzyme and also the host cell serine protease TMPRSS2 in the infected cells[7,8].

With the rapid expansion of SARS-CoV-2 the development of data and tools to understand its immune responses became necessary. Bioinformatics tools accessible for structure analysis of the TPO amino acids (AA) provide an essential structure to understand its molecular mechanisms. At the same time, molecular modeling has led to the understanding of molecular mimicry as a result of human TPO's cross-mediated immune response with Sars cov2, since most molecular mimicry probably involves the mediation of T cells, and T cells recognize linear peptides ranging from 8 to 20 AA[9].

In this study, we evaluated the structural similarity of the AA sequence between TPO and COVID-19, using bioinformatics tools, to propose a mechanism that could explain the production of autoantibodies with cross-reaction between TPO and COVID-19.

METHODOLOGY

We carry out the comparison between the AA sequence of the TPO human and COVID-19, accessible in database of National Center for Biotechnology Information (NCBI) on Basic Local Alignment Search Tool (TBLASTN)[10]. TBLASTN is a program of operation for BLAST used to generate alignments between protein sequence and nucleotide translated in six frames.

The expect value is an indicator that represents the number of hits one can expect to recognize by chance when searching a database of a specific sample (expect value is considered statistically significant when p<0.05). The expect value decreases exponentially as the punctuation of the match increases. The lower an expect value is, or the closer it is to zero, the more significant the match is. However, identical short alignments have relatively high E values.

This occurs depending on the calculation of the E value take into account the size of the consulted sequence. The high expected values make sense because short sequences are more likely to occur in the database purely at random. Thus, the expected value can also be used as a timely means of creating a significance limit to describe the results.

- **Homology sequence analysis**

The homology analysis of a sequence is a method of evaluating sequence databases using alignment with a query sequence. By statistically evaluating how much the database and the query sequences correspond, it is possible to infer in the homology, transferring data to the query sequence.

The alignment between SARS COV2 sequences, referred to as "sbjct" sequence and TPO sequences referred to as "query" was used a protein/nucleotide alignment method with the TBLASTN program. TBLASTN act by translating database nucleotide sequences to hypothetical AA sequences in all six reading frames and posteriorly aligns the hypothetical AA sequences to the query.

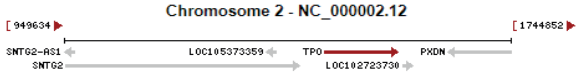
The following TPO AA sequence was analyzed, with the respective NCBI sequence identification number: thyroid peroxidase [Homo sapiens]=AAA61217.2. The following COVID-19 AA sequences were analyzed, with the respective NCBI sequence identification numbers: Chain A, SARS-COV-2 spike glycoprotein=6XEY_A, Chain B, SARS-COV-2 spike glycoprotein=6XEY_B, and Chain C, SARS-COV-2 spike glycoprotein=6XEY_C.

RESULTS

- Thyroid peroxidase [Homo sapiens]

The TPO accession number: AAA61217.2 the ID contained 922 AA in its protein sequence[11]. The TPO gene contains 17 exons and covers at least 150 kb of chromosome 2 (Figure 1)[12].

Figure 1 – *TPO gene*

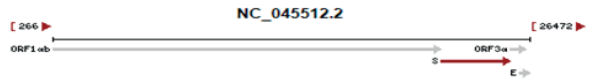


Source: https//www.ncbi.nlm.nih.gov/gene/?term=AAA61217.2 - Public domain

- COVID-19

The COVID-19 accession number: 6XEY_A, the ID contained 1288 AA in its protein sequence[13], 6XEY_B, the ID contained 1288 AA in its protein sequence[14], and 6XEY_C, the ID contained 1288 AA in its protein sequence[15]. The genomic sequence: NC_045512.2 (Figure 2).

Figure 2 – *Genomic sequence SARS-CoV-2 spike glycoprotein*

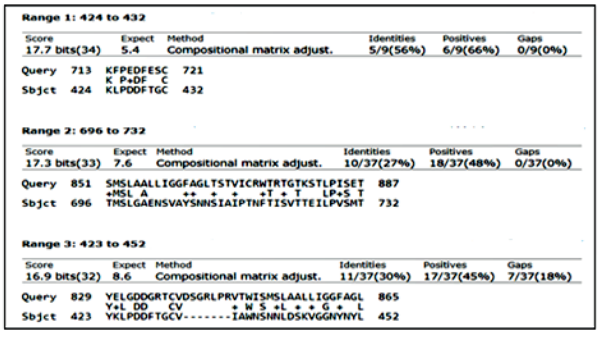


Source: https://www.ncbi.nih.gov/gene/43740569 - Public domain

To find the sequence homologies between TPO and COVID-19, the three SARS-CoV-2 spike glycoprotein sequences was compared the TPO sequence. The sequence was compared using the query sequence-based multiple sequence alignment produced by TBLASTN tool.

The identity value affords the degree of similarity between the "sbjct" and "query", considering the number of gaps. The homologies between the TPO and COVID-19 ranged from 27.0 % (10 identical residues out of 37 AA in the sequence) to 56.0% (5 identical residues out of 9 AA in the sequence). The identical alignments presented relatively high expect values due to presence of short alignment. The alignment between TPO and COVID-19 detected in this study is showed in Figure 3.

Figure 3 – *Alignment between TPO and COVID-19*



Range 1: 424 to 432

Score	Expect	Method	Identities	Positives	Gaps
17.7 bits(34)	5.4	Compositional matrix adjust.	5/9(56%)	6/9(66%)	0/9(0%)

```
Query  713  KFPEDFESC  721
            K P+DF  C
Sbjct  424  KLPDDFTGC  432
```

Range 2: 696 to 732

Score	Expect	Method	Identities	Positives	Gaps
17.3 bits(33)	7.6	Compositional matrix adjust.	10/37(27%)	18/37(48%)	0/37(0%)

```
Query  851  SMSLAALLIGGFAGLTSTVICRWTRTGTKSTLPISET  887
            +MSL A      +  +  +  +T + T   LP+S T
Sbjct  696  TMSLGAENSVAYSNNSIAIPTNFTISVTTEILPVSMT  732
```

Range 3: 423 to 452

Score	Expect	Method	Identities	Positives	Gaps
16.9 bits(32)	8.6	Compositional matrix adjust.	11/37(30%)	17/37(45%)	7/37(18%)

```
Query  829  YELGDDGRTCVDSGRLPRVTWISMSLAALLIGGFAGL  865
            Y+L DD   CV        + W S +L + + G +  L
Sbjct  423  YKLPDDFTGCV-------IAWNSNNLDSKVGGNYNYL  452
```

Source: Search result

Length of 933 of TPO protein tandem repetitive sequence of genomic with 56% (5 identical residues out of 9 AA in the sequence) was accessed. The complementary nucleotide sequences were: 27% (10 identical residues out of 37 AA in the sequence), and 30% (11 identical residues out of 37 AA in the sequence), homologous to COVID-19. The identical alignments presented relatively high expect values due to presence of short alignment.

Tandem repeats happen in DNA whenever a standard of one or more nucleotides is replicated and the replications are exactly contiguous to each other. However, in proteins, perfect tandem repetitions are uncertain in the largest number of in vivo proteins, and most of the studied replications are in proteins that have been programmed[16].

DISCUSSION

Our study suggests a possible immunological link between COVID-19 and TPO, since the sequence homology between COVID-19 and TPO could present a possible molecular mimicry which could be a mechanism to induce an initial immunological cross-reaction between self-antigens triggering autoimmune thyroiditis.

Several pathogenic viruses have been proposed for the triggering and development of autoimmune diseases. Thus, possibly COVID-19 may also be involved with autoimmune diseases, as well as other viruses that have been implicated in the triggering of autoimmune diseases[17]. Have been reported rates of thyrotoxicosis significantly higher in subjects with COVID-19, signaling for an atypical form of thyroiditis associated to the SARS-CoV-2 infection[18].

The polarized T helper (Th) cells, called Th1 and Th2, have well-defined profiles, and Th1 cells are involved in organ-specific autoimmunity, such as thyroid autoimmune diseases. Thus, the development of autoimmunity secondary to vaccination or infection is most often related to antigenicity[19]. Epidemiological data show that viral and/or microbial infections usually precede autoimmune diseases[20].

Three types of molecular mimicry are described: the first type of molecular mimicry involves identical amino acid sequences associated between different molecules present in microorganisms and the tissues. The second type of molecular mimicry determined by the antibody identification of similar structures sharing regions with 40.0% of identities or less and cross-reactive local are not fully identical. The third type of molecular mimicry is evidenced in immunological cross-reactions between molecules as diverse as proteins and DNA or peptides and carbohydrates[21].

We analyzed the sequence homology between the AA sequences of one human TPO and of the Chain A, Chain B, and Chain C of the COVID-19. Our study observed that TPO and COVID-19 present AA sequences homologies, where in some similar regions contain epitopes of both TPO and COVID-19 very similar. We did not find in the medical literature studies that evaluated the homology of the AA sequence between TPO and COVID-19.

The FASTA and TBLASTN tool of sequence comparison programs generate systems to check protein and nucleotides sequences in your database[22]. TBLASTN was used to identify homologous structures and AA sequences based on the similarity of excess sequences between TPO and COVID-19. The expected value is a measure to describe the number of cases expected at random when doing a database search of a defined size. It decreases exponentially as the score of the match increases. In this study, identical alignments presented relatively high expected values due to short alignment.

Due to the limitations of the unavailability of more comprehensive data on the proteins and nucleotides researched, because the TBLASTN is a limited method to search for linear epitopes homologies, losing three-dimensional conformational homologies and possible cross reactivity between protein and nonprotein epitopes, the homologies between the AA sequences of TPO, which are potential B and T cell epitopes of these antigens, and COVID-19 proteins, were well identified. Thus, these

observed homologies can be functionally important in molecular mimicry, receptor binding and cellular signaling events involved in autoimmunity, and can have important implications for understanding the relationship between autoimmune thyroiditis and COVID-19 due to the formation of equivalent autoantibodies.

CONCLUSION

Bioinformatics data suggest a possible immunological link between autoimmune thyroiditis and COVID-19. The homologies between COVID-19 and thyroid self-proteins by molecular mimicry could be a mechanism of induction of a cross reactive immune response to self-antigens resulting in autoimmune thyroiditis. However, our sample for homology evaluation was small, and further research is needed to understand the true impact to support this theory.

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