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Article

Molecular Mimicry between SARS-CoV-2 and Human Endocrinocytes: A Prerequisite of Post-COVID Endocrine Autoimmunity

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Abstract: Molecular mimicry between human and microbial/viral/parasite peptides is common and for a long time is associated with the etiology of autoimmune disorders provoked by exogenous pathogens. Increasing evidence accumulated from the past years suggests a strong correlation between the SARS-CoV-2 infection and autoimmunity. The article analyzes the immunogenic potential of the peptides shared between SARS-CoV-2 spike glycoprotein (S-protein and antigens of human endocrinocytes involved in most common autoimmune endocrinopathies. Totally the study revealed 14 pentapeptides shared by S-protein of SARS-CoV-2 and autoantigens of thyroid, pituitary, adrenal cortex and Langerhans' islets beta-cells, 12 of them belong to immunoreactive epitopes of SARS-CoV-2. The discussion of the data links the results with clinical correlates of COVID-associated autoimmune endocrinopathies. Most common of them is an autoimmune thyroid disease, so the majority of shared pentapeptides belong to marker autoantigens of this disease. Most important in pathogenesis of severe COVID-19, according authors' opinion, can be autoimmunity against adrenals, because their adequate response prevents from excessive systemic action of inflammatory mediators which cause cytokine storm and hemodynamic shock. The criticism of antigen mimicry concept is given with a statement that peptide sharing is not a guarantee, but just a prerequisite of autoimmunity excess provocation. The last event occurs in carriers of certain HLA haplotypes and in case when shared peptide is used in antigen processing only [1 figure, 5 tables, bibliography 38 references].

Keywords: SARS-CoV-2; COVID-19; autoantibodies; autoimmune endocrinopathies; long-COVID syndrome; molecular mimicry; thyroid gland; adrenals; pituitary; Langerhans' islets

1. Introduction

In the beginning of 20th century a Russian biologist, alumnus of Saint Petersburg University Konstantin S. Merezhkovsky([6], [6]) suggested that *Cyanobacteria* gave rise to chloroplasts and *Proteobacteria* transformed into mitochondria of eukaryotic cells. An element of his avant-garde endosymbiotic concept was an idea that proteins of microorganisms and higher eukaryotes may be similar or even partially identical because of their common evolutionary origin (Fig. 1).

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Figure 1. Konstantin Sergeevich Merezhkovsky (aka: Mereschkowski, Mereschkowsky), an originator of symbiogenetic theory and antigen mimicry ideas (Photo from the collection of the Saint Petersburg State University Zoological Museum).

Much later this idea was adopted by immunologists and gave birth to the concept of molecular mimicry as a prerequisite for pathological autoimmunity, provoked by shared antigens of exogenous pathogens.

First it was suspected for antigens of *Streptococci* and etiology of rheumatic fever [6], particularly the homology of polysaccharide antigens from hemolytic *Streptococci* and those of cardiac valves, resulted in development of rheumatic endocarditis after streptococcal infection. Then the phenomenon was explained by an American biologist Raymond T. Damian (who suggested the very term "molecular mimicry") as an element of the evolutionary strategy of germs' disguise while escaping host's immune response [6]. Later the concept was spread on viral antigens promoting autoimmune diseases [6]. The early imaginations about the cross-reactivity of antigens were confined with the hypothesis that three-dimensional space conformation of some alien antigens has to resemble spatial conformations of autoantigens, thus provoking anti-self action of anti-alien antibodies. But, later it was shown that such a similarity is exclusively rare. Yet, it is still believed that this particular kind of cross-reaction (e.g. in conformational determinants of human and *Trypanosoma cruzi* glycolipids) causes some autoimmune complications of Chagas disease [6]. Much more often there occurs a cross-reaction between sequential determinants of autoantigens and alien antigens because the evolutionary diversity of primary structures in these polypeptides is not so great, as for spatial tertiary conformations. It is the close resemblance of short peptides, processed and presented by antigen presenting cells of predisposed individuals to their T-cells [6].

Many phenomena of this kind are well-documented and have utmost clinical significance. For example, in HLA II D_3 and D_4 positive individuals, the epitopes from some viruses (Coxsackie B_4, ECHO, rubella virus, mumps paramyxovirus) may serve as viral diabetogens or triggers for autoimmune insulitis and subsequent diabetes mellitus type I [6]. Anti-alien Th cells in this phenomenon may promote the anti-self immune responses.

An additional charm this concept gained when idiotype-antiidiotypic theory of immune regulation appeared, and an American scientist Paul H. Plotz coined an idea that there may exist not only direct molecular mimicry of viral and self peptides, but also immunologic mirror imaging ("casting") of key viral epitopes (responsible for interaction of virus with a target cell) by anti-idiotypic autoantibodies, generated during self regulation of anti-viral immunity [6]. It was confirmed also for bacterial antigens on the model of peptide sharing between *Yersinia enterocolytica* and TSH receptor, which appeared to be

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essential for etiology of Graves' disease [7]. Generally speaking, in molecular mimicry a cross-reacting epitope of some germ may increase the low concentration of an autoantigen and expression of co-stimulatory molecules on immune cells to the level, sufficient for activation of peripheral anergic T-clones, thus facilitating their affinity to antigen presenting cells, thus elongating the existence and effectiveness of immuno-synapse formed between them. In other words, what was ignored according "danger model" [7], due to antigenic mimicry starts to elicit noticeable and even pathogenic autoimmune response.

Nowadays the concept of molecular mimicry is applied even broader, enrolling not only microbial, but also animal antigens penetrating into human body. Thus, a cross-reaction of cow milk albumin and human insulin epitopes is essential for development of some cases of insulin-dependent diabetes mellitus in catamnesis of non-breast fed HLA II D_3 and D_4 positive babies, whose gut is able to absorb short peptides during first 4-5 months of extra-uterine life [7]. Moreover, the close homology between saliva antigens of local flies and antigens of human skin is suggested as a key mechanism of endemic autoimmune pemphigus occurring in Brazil and Tunisia [7].

The pandemic Coronavirus disease 2019 (COVID-19) is caused by a single-stranded, positive-sense RNA genome containing enveloped virus SARS-CoV-2. By July 2022, globally almost 572 mln. people have been infected [7]. The host immune response to SARS-CoV-2 appears to play a critical role in the disease pathogenesis as well as in clinical manifestations, outcomes and complications. SARS-CoV-2 not only activates antiviral immune response, but also may provoke excessive systemic action of cytokines anf other pro-inflammatory mediators, accompanied by lymphopenia and lymphocyte dysfunction as well as granulocyte and monocyte abnormalities [7]. Increasing evidences accumulated through the past 2 years suggest a strong correlation between the SARS-CoV-2 infection and autoimmunity. Virtually, SARS-CoV-2 looks like a "virus of autoimmunity" taking into account high incidence and broad spectrum of its autoimmune complications, including prolonged and remote ones observed in post-COVID syndrome/long COVID [7].

The role of peptide resemblance in COVID-19 related autoimmune disorders provocation was suspected in the first months of pandemic by Yehuda Shoenfeld and Francesco Cappello ([7], [7]). Several attempts gave promising results as regards to shared peptides of SARS-CoV-2 spike (S-) glycoprotein versus various host antigens: Human lung surfactants [7], neuronal proteins of respiratory pacemaker [7], olfactory receptor, and proteins expressed by endothelium or leukocytes [7]. All that data were interpreted in view of pathogenesis of appropriate manifestations of acute COVID-19, like respiratory failure, anosmia, vascular/thrombotic disorders and lymphopenia. But, nowadays the problem of long COVID or post-COVID syndrome became quite relevant due to numerous cases of prolonged health disorders after recuperation from acute COVID-19, even not severe one. Many manifestations of post-COVID syndrome resemble closely those resulted from the disorders of neuroendocrine regulation. SARS-CoV-2 *per se* is able to alter many neuroendocrine targets expressing the receptors used by virus as entrance gates [7]. Autoimmune involvement of neuroendocrine organs in post-COVID is also probable, although much less studied [7]. Molecular mimicry of immunodominant SARS-CoV-2 proteins and immunogenic epitopes of endocrinocytes may contribute into autoimmune mechanistic links of post-COVID health disorders. But, so far it has not been explored enough. There is only one pilot bioinformatics study of peptide sharing between SARS-CoV-2 and pituitary-adrenal targets, performed by Churilov *et al.* [7].

In this article we report the data of bioinformatic analysis of possible molecular mimicry between SARS-CoV-2 S-protein and those autoantigens of human endocrinocytes typical for most important autoimmune endocrinopathies.

2. Material and methods

Peptide sharing between proteins of human endocrinocytes (thyroid gland, adrenals, pituitary and Langerhans' islets β-cells) and spike glycoprotein (UniProt, Id= P0DTC2) from SARS-CoV-2 was analyzed using pentapeptides as sequence probes since it is a peptide grouping formed by at least five amino acid residues which defines a minimal

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immune determinant able for highly specific antibodies induction, as well as that framing the antigen specific interactions of immune cell receptors [7]. A library of human proteins expressed by endocrinocytes was assembled from UniProtKB database [7].

We selected the following proteins most commonly serving as targets in several frequent endocrinopathies, according current clinical and experimental data [6]: targets of autoimmune thyroid disease [*Thyroid peroxidase (P07202); Thyrotropin receptor (P16473);* and *Thyroglobulin (P01266)*], of autoimmune Addison's disease [*21-hydroxylase, CYP21A2 (P08686)*], of diabetes mellitus type 1 [*Islet-cell autoantigen 1, IA-1 (Q16849); IA-2 or protein thyrosine-phospatase receptor-type N, PTPRN (Q16849); Glutamate decarboxylase, GAD67 (Q99259); Insulin (P01308), Carboxypeptidase H (P16870);* and *Zinc transporter 8, ZnT8 (Q8IWU4)*] and of autoimmune (lymphocytic) hypophysitis/infundibulohypophysitis [*Prolactin* (*P01236*); *α-enolase* (*P06733*); *Rabfillin 3a* (*Q9UNE2*); *Cytotoxic T-lymphocyte antigen-4*, CTLA-4 (*P16410*); and *Proopiomelanocortin* (*P01189*)].

The S-protein primary sequence was dissected into pentapeptides offset by one residue (that is: MFVFL, FVFLV, VFLVL, FLVLL and so forth) and the resulting viral pentapeptides were analyzed for occurrences within the human proteins mentioned above. Occurrences and the corresponding proteins were annotated.

The immunological potential of the peptides shared between SARS-CoV-2 spike glycoprotein and proteins of endocrinocytes was analyzed by searching the Immune Epitope DataBase and Analysis Resource [7] for immunoreactive SARS-CoV-2 spike glycoprotein epitopes hosting the shared pentaptides. We also used the database of the National Center of Biotechnology Information [7].

3. Results

Quantitatively, SARS-CoV-2 spike glycoprotein was found to share 14 minimal immune determinants, i.e., pentapeptides, with 8 human proteins expressed by endocrinocytes and involved in pathogenesis of clinical autoimmune endocrinopathies.

The shared pentapeptides are described in Tables 1 – 4 below. All of them present in immunoreactive SARS-CoV-2 epitopes (Table 5). Pentapeptides of immunoreactive epitopes are written in all tables with **bald** letters.

Table 1. Molecular mimicry of S-protein with autoantigens of type 1 diabetes mellitus.

Langerhans' islets β-cell autoantigens	**Shared pentapeptides**
PTPRN (Q16849)	**LPPLL**
Islet cell autoantigen 1 (Q05084)	**GYQPY, LDPLS**
GAD67 (Q99259)	**AGAAL, VGYQP**
Carboxypeptidase H (P16870)	**SALLA**

Other β-cell autoantigens explored did not share any pentapeptides with SARS-CoV-2 S-protein.

Table 2. Molecular mimicry of S-protein with an autoantigen of Addison's disease.

Autoantigen of adrenocorticocytes	**Shared pentapeptides**
CYP21A2 (P08686)	**LQDVV**

Table 3. Molecular mimicry of S-protein with the autoantigens of autoimmune thyroid disease.

Thyroid autoantigens	**Shared pentapeptides**
Thyroid peroxidase (P07202)	**RAAEI**
Thyrotropin receptor (P16473)	**ICGDS, LLPLV**
Thyroglobulin (P01266)	**FNFSQ, SAIGK, LDSKT**

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Table 4. Molecular mimicry of S-protein with a pituitary autoantigen.

Pituitary autoantigen	**Shared pentapeptides**
Prolactin (P01236)	**SNLLL**

Other pituitary autoantigens checked did not share any pentapeptides with SARS-CoV-2 S-protein.

Exploration of the Immune Epitope DataBase revealed that all the shared pentapeptides described in Table 5, are also presented in SARS-CoV-2 spike glycoprotein–derived epitopes that have been experimentally validated as immunoreactive ones [7].

Table 5. Immunoreactive SARS-CoV-2 spike glycoprotein-derived epitopes containing pentapeptides shared between the S-protein and proteins of human endocrinocytes.

IEDB ID of an immunoreactive epitope	**Epitope Sequence**
1125063	gltv**LPPLL**
1309589	sygfqptngv**GYQPY**rvvvl
1074866	ca**LDPLS**etk
531783	g**AGAAL**qipfamqma
1074866	ca**LDPLS**etk
1310448	gk**LQDVV**nqnaqaln
100428	qli**RAAEI**rasanlaatk
1310877	vdctmy**ICGDS**tecs
1071273	**LLPLV**ssqcvnlttr
1087679	pikdfgg**FNFSQ**ilpdps
1071651	nqfn**SAIGK**iqdsls
1075075	t**LDSKT**qsl
1069347	dstec**SNLLL**qygsf
1496254	qyt**SALLA**gtit
1309589	sygfqptng**VGYQP**yrvvvl

4. Discussion

Half of shared pentapeptides revealed in our study belong to marker autoantigens of autoimmune thyroid disease, namely both its forms: Hashimoto's thyroiditis and Graves' disease. It is not surprising that provocation of new cases of this diseases and exacerbation of existing autoimmune thyroid disorders is not rare in COVID-19 patients. For example, a Turkish authors recently summarized clinical descriptions of at least 20 of such cases [7].

Although relations between diabetes mellitus type 1 and COVID-19 are somewhat contradictory, and new onset cases should be clearly distinguished from simple stress-related and glucocorticoid treatment derived hyperglycaemia [7], there is enough witnesses that new *Coronavirus* infection may alter Langerhans' islet β-cells, aggravate existing type 1 diabetes mellitus and occasionaly even provoke its debute [7]. The last illness in its fulminant variant was also described after anti-COVID vaccination [7]. These facts determine the pathogenic interpretation of our data on common pentapeptides of four different diabetic autoantigens and S-protein of SARS-CoV-2.

Of special interest is the existence of immunogenic epitope sharing between a marker autoantigen of the autoimmune adrenalitis – 21-hydroxylase – and S-protein of SARS-CoV-2. The proper adrenocortical response in acute COVID-19 is a critically important defensive mechanism against vicious consequences of cytokine storm, which otherwise may result in hemodynamic shock. Glucocorticoids are effective in treatment of severe COVID-19 [7]. That's why earlier we coined an idea that anti-adrenal autoimmunity can be one of the crucial links in pathogenesis of severe and fatal COVID-19 cases [7]. Adrenal insufficiency of mixed primary and secondary origin is not rare both in acute COVID-19 and in post-COVID syndrome and was registered even earlier, in epidemic caused by another *Coronavirus*: SARS-CoV-1 [7]. Lymphocytic infiltration of suprarenal glands similar

to that of autoimmune Addison's disease was registered in fatal cases of COVID-19 [7]. In a pilot study of 2021 we demonstrated the sharing of several pentapeptides between SARS-CoV-2 S-protein and human adrenocortical receptors (of ACTH and angiotensins), but absence of such homology with ACTH [7]. Now a key enzyme of adrenocortical steroidogenesis can be added to the list of *Coronavirus* mimics in adrenal cortex.

In spite of several works on pituitary involvement in COVID-19 [7] and even descriptions of the cases of lymphocytic hypophysitis or infundibulohypophysitis in COVID-19 ([7], [7]), our data on peptide sharing with SARS-CoV-2 regarding pituitary antigens are very scarce. Previously we failed to find peptide sharing between SARS-CoV-2 and proopiomelanocortin [7] and now the majority of pituitary autoantigens checked, except for prolactin only, also did not display antigen mimicry with SARS-CoV-2 S-protein.

Of course, just the presence of any shared peptide in a pathogen, even within epitopes considered to be immunoreactive, is not yet a guarantee of autoimmunity excess provocation. It is only a prerequisite for it. The most essential is in what individual HLA context these peptides will be presented, because different HLA haplotypes cause various processing of the same protein by different individuals. Figuratively speaking, the difference of self and non-self proteins, being relative, can be more or less obvious to lymphocytes, depending on HLA set, like in jewelry art - the impression, produced by the same precious stone depends greatly from its mounting design and metal chosen, not only from the properties of gem itself. That's why, sequence homology, even extensive one, revealed by bioinformatics, does not necessarily lead to immunologic cross-reactivity, confirmed by "wet lab" methods, which was demonstrated, for example, in autoimmune primary biliary cirrhosis between human pyruvate dehydrogenase and urease-β from *Helicobacter pylori* [7]. Moreover, it may cause real cross-reactiivity in some individuals and fail to do it in others [7].

Aristo Vojdani et al. [7] checked the real ability of 55 various human autoantigens sharing peptides with SARS-CoV-2 (among them few of those explored in our study also) to interact with anti-SARS-CoV-2 monoclonal antibodies against S-protein and against other SARS-CoV-2 antigens. The study registered moderate immunologic cross-reactivity of antibodies towards S-protein with human thyroid peroxidase and glutamic decarboxylase, weak one with thyroglobulin and no cross-reactivity with enolase and insulin, which is generally in agreement with our data.

We consider bioinformatic analysis an essential step in preliminary evaluation of autoimmunity risks and spectrum in COVID-19 complications, including post-COVID syndrome. Also it may be useful in epitope selection for elaboration of most safe anti-COVID vaccines.

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