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BRIEF REPORT

СЦ2в - скраћеница за САРС-ЦоВ-2

Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: implications for the vaccine

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Ова студија пореди пептидне секвенце СЦ2в и разних врста сисара. Водили смо се логиком да ако је тачно да је молекуларна мимикрија између СЦ2в и хуманих протеина један од разлога за ковид-19, онда различити облици молекуларне мимикрије треба да постоје између вируса и разних животиња...концензус је такав да не постоји доказ који показује да заражени кућни љубимци могу бити извор СЦ2в заразе за људе или друге љубимце.

Introduction

The ethiopathology of the diseasome induced by the SARS-CoV-2 infection in the human host [1] is under intensive investigation. A likely mechanism is that the multitude of the diseases encompassed within COVID-19 derives from molecular mimicry phenomena between the virus and human proteins [2]. The rationale is that, following an infection, the immune responses raised against the pathogen can cross-react with human proteins that share peptide sequences (or structures) with the pathogen, in this way, leading to harmful autoimmune pathologies [3, 4]. Accordingly, lungs and airways dysfunctions associated with SARS-CoV-2 infection might be explained by the sharing of peptides between SARS-CoV-2 spike glycoprotein and alveolar lung surfactant proteins [2]. In support of this thesis, additional reports [5–8] highlight molecular mimicry and cross-reactivity as capable of explaining the SARS-CoV diseases. Of special interest, cross-reactive T cell recognition between circulating "common cold" coronaviruses and SARS-CoV-2 has been also suggested [9].

In this scientific framework, this study comparatively analyzed the peptide sharing between SARS-CoV-2 and mammalian species. Our reasoning is that if it were true that molecular mimicry between SARS-CoV-2 and human proteins contributes to or causes COVID-19, then different levels/patterns of molecular mimicry vs. the virus should characterize the various animal species. Indeed, scarce data exist to indicate that domestic animals, for instances dogs and cats, can either transmit the virus or develop the virus-associated diseasome [10]. In general, currently, the consensus remains that there is no evidence that infected pets are a source of SARS-CoV-2 infection for people or other pets [11, 12].

Based on this rationale and using hexa- and heptapeptides as sequence probes [13–15], the peptide overlap between SARS-CoV-2 spike glycoprotein and mammalian proteomes was analyzed.

Сходно томе, поремећај рада плућа и плућних путева у случају СЦ2в инфекције може се објаснити тиме да пептиди спајк гликопротеина и пептиди алвеоларног суфрактант-протеина деле исту секвенцу (чиме бивају препознати од истог антитела).

1

Peptide sharing analyses have been extensively described elsewhere [16, 17]. Briefly, SARS-CoV-2 spike glycoprotein (NCBI protein Id=QHD43416.1) primary sequence was dissected into hexa- and heptapeptides offset by one residue (i.e., MFVFLV, FVFLVL, VFLVLL, FLVLLP). We obtained 1268 hexapeptides and 1267 heptapeptides. Then each viral hexa- or heptapeptide was analyzed as a probe to scan for occurrences of the same hexa- or heptapeptide in the reference proteome from the following mammalian organisms (with taxonomy ID in parentheses): human, *Homo sapiens* (9606); mouse, *Mus musculus* (10090); rat, *Rattus norvegicus* (10116); cat, *Felis catus* (9685); dog, *Canis lupus familiaris* (9615); rabbit, *Oryctolagus cuniculus* (9986); chimpanzee, *Pan troglodytes* (9598); gorilla, *Gorilla gorilla gorilla* (9595); and rhesus macaque, *Macaca mulatta* (9544). Three viral proteomes were added as coronavirus controls: human coronavirus HKU1 (290028); human coronavirus 229E (11137); and human coronavirus OC43 (31631). The hexa/

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Већ постоји предлог да унакрсно-реактивне Т ћелије које препознају коронавирусе "обичне прехладе", исто тако могу да препознају и СЦ2в (антигене).

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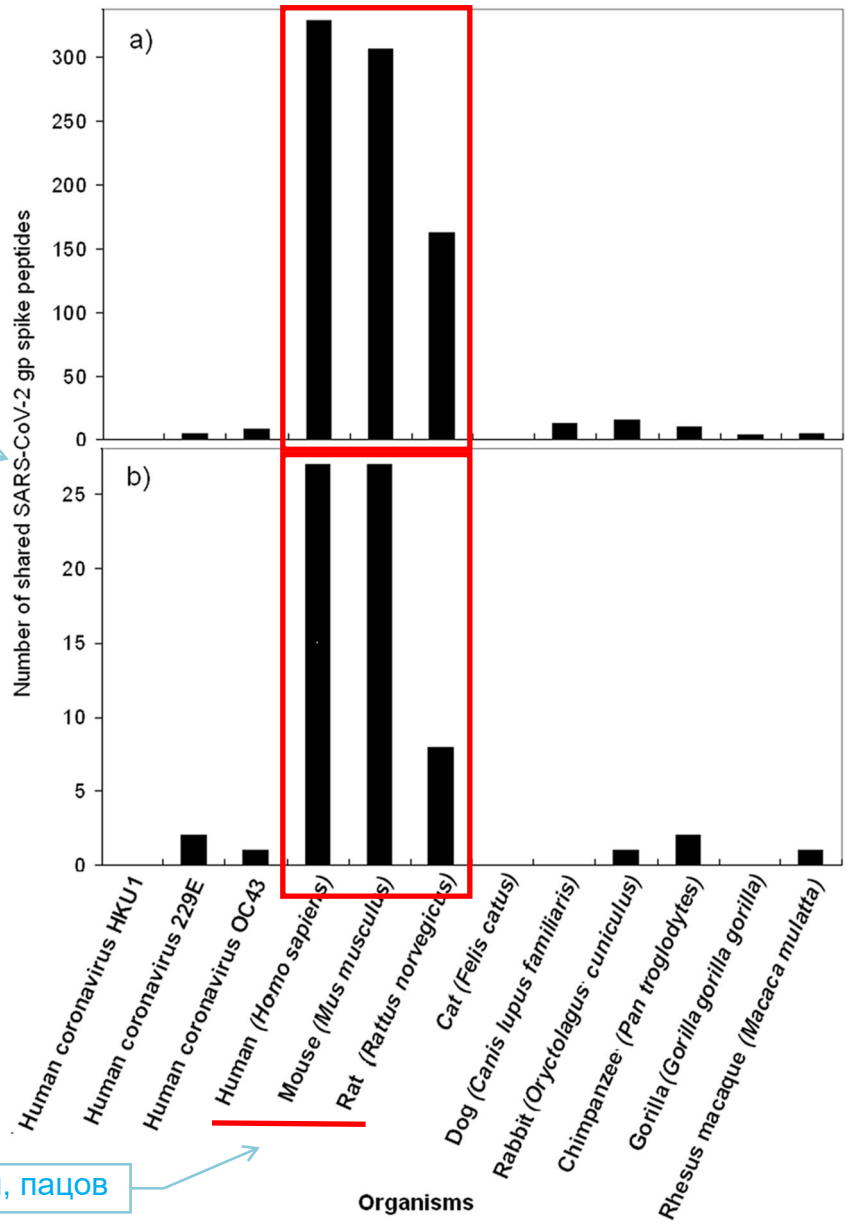

Број пептида датог организма који су слични СЦ2в

Човек, миш, пацов

Fig. 1 Peptide sharing between SARS-CoV-2 spike glycoprotein and mammalian and coronavirus proteomes. **a** Peptide sharing at the 6-mer level. **b** Peptide sharing at the 7-mer level

heptapeptide matching analyses were conducted by using Pir Peptide Matching program [18].

The expected value for hexapeptide sharing between two proteins was calculated by considering the number of all possible hexapeptides. Since in a hexapeptide, each residue can be any of the 20 amino acid (aa), the number of all possible hexapeptides N is given by $N = 20^6 = 64 \times 10^6$. Then, the number of the expected occurrences is directly proportional to the number of hexapeptides in the two proteins and inversely proportional to N. Assuming that the number of hexapeptides in the two proteins is $<< N$ and neglecting the relative abundance of aa, we obtain a formula derived by approximation, where the expected number of hexapeptides is $1/N$ or 20^{-6}. By applying the same calculation, the expected value for heptapeptide sharing between two proteins is equal to 20^{-7}.

Велики број хептапептида је сличнан између СЦ2в спајк гликопротеина и (разних) протеина човека. Ова сличност је неочекивана, са математичке тачке гледишта мало је вероватна, обзиром да је вероватноће истоветности само једног хептапептида између два протеина x = 20 на минус 7 (1 у 1 280 000 000), односно за хескапептид, x = 20 на минус 6 (1 у 64 000 000).

Results

The graphical illustration of the peptide sharing between SARS-CoV-2 spike glycoprotein and the analyzed mammalian and coronavirus proteomes is reported in Fig. 1. The hexa- and heptapeptide sequences involved in the sharing are detailed in Tables S1 and S2, respectively.

Figure 1 shows that:

- A massive heptapeptide sharing exists between SARS-CoV-2 spike glycoprotein and human proteins. Such a peptide commonality is unexpected and highly improbable from a mathematical point of view, given that, as detailed under the "Methods" section, the probability of the occurrence in two proteins of just one heptapeptide is

У периоду од јануара до јуна, што укључује првих 12 недеља након месеца марта и проглашења пандемије, мање од 20 случајева љубимаца је било позитивно на СЦ2в.

Када су у питању домаће животиње, коронавируси су познати као енетерични (цревни систем) патогени мачака, паса, крава и свиња. Ипак, изгледа да коронавируси нису патогени вируси за домаће животиње и љубимце.

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equal to ~ 20^{-7} (or 1 out of 1,280,000,000). Likewise, the probability of the occurrence in two proteins of just one hexapeptide is close to zero by being equal to ~ 20^{-6} (or 1 out of 64,000,000).

- На конто података са фигуре 1 и узимајући у обзир старост и стање здравља, само мишеви у старијем добу живота могу бити прави експериментални модел за тестирање анти-СЦ2в спајк гликопротеинске вакцине, када је у питању хумана употреба.
-
- Likewise, the proteomes of the three human coronaviruses HKU1, 229E, and OC43, which were used as viral controls, have no or only a few peptides in common with the spike glycoprotein. In this regard, it seems that the SARS-CoV-2 spike glycoprotein is phenetically more similar to humans and mice than to its coronavirus "cousins".

2

Протеоми (листа свих протеина) три коронавируса ХКУ1, 229Е и ОЦ43, који су узети као контролна група вируса, имају тек по неки или немају заједничке пепиде са спајк гликопротеином СЦ2в. Испада да је спајк гликопротеин СЦ2в "сличнији" човековим и мишјим протеинима, него својим корона-рођацима.

Conclusions

This study thoroughly quantifies the hexa- and heptapeptide sharing of SARS-CoV-2 spike glycoprotein—which is a major antigen of the virus—with mammalian proteomes. A massive peptide commonality is present with humans and mice, i.e., organisms that undergo pathologic consequences following SARS-CoV-2 infection. Instead, no or a lowest number of common peptides are present in mammals that have no major pathologic sequelae once infected by SARS-CoV-2 [10–12]. Hence, the data appear to be an indisputable proof in favor of molecular mimicry as a potential mechanism that can contribute to or cause the SARS-CoV-2 associated diseases [8].

Нема или је јако мало заједничких пептида са СЦ2в код оне групе сисара који немају значајне последице након инфекције СЦ2в-ом.

tudy indicates that the choice of the laboratory animals to be used in preclinical studies during the formulation/validation of anti-pathogen vaccines. In the case in object, given the lowest level of sequence similarity of SARS-CoV-2 spike glycoprotein vs. primates proteins, results obtained in studies that use primates as animal models, i.e., rhesus macaque [19], would be unreliable because of the impossibility of verifying the occurrence of cross-reactivity and related autoimmunity in the absence of shared sequences. In this regards, data illustrated in Fig. 1 explain why, as highlighted by Hogan [20], "SARS-CoV infection of cynomolgus macaques did not reproduce the severe illness seen in the majority of adult human cases of SARS" [21]. Actually, no clinical signs of disease or marked lung pathology were seen in a study in which both rhesus and cynomolgus macaques were infected with SARS-CoV [22], and the Authors' conclusion is that the macaque model is of limited utility in the study of SARS and the evaluation of therapies. Likewise, McAuliffe et al. [23] described similar findings: "SARS-CoV administered intranasally and intratracheally to rhesus, cynomolgus and African Green monkeys replicated in the respiratory tract but did not induce illness".

As for domestic animals and cattles, coronaviruses are long known to be enteric pathogens of cats (FeCoV), dogs (CaCoV), cattle (BCoV), and swine (TGEV) [24]. Nonetheless, coronaviruses do not appear to be pathogenic for domestic animals and cattles. Indeed, the scarce or null susceptibility to SARS-CoV-2-induced pathologies is certified by the American Veterinary Medical Association that verbatim declares: "during the first five months of the COVID-19 outbreak (January 1 – June 8, 2020), which includes the first twelve weeks following the March 11 declaration by the WHO of a global pandemic, fewer than 20 pets have tested positive, with confirmation, for SARS-CoV-2 globally. This despite the fact that as of June 8, the number of peopl
globally
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ВАЖНО: Само вакцине које су базиране на минималним имунским детерминантама специфичним за патогене а које нису присутне у човековим протеинима, могу да послуже као основ за сигурну и учинковиту вакцину, без бојазни за могућу аутоимуну реакцију.

In conclusion, in light of the data exposed in Fig. 1 and given the susceptibility parameters such as aging and health status, only aged mice appear to be a correct animal model for testing an anti-SARS-CoV-2 spike glycoprotein vaccine to be used in humans [25, 26].

Finally, this study once more reiterates the concept that only vaccines based on minimal immune determinants unique to pathogens and absent in the human proteome might offer the possibility of safe and efficacious vaccines [16, 27–30].

Compliance with ethical standards

Conflict of interest DK declares no conflicts. YS appears as a medical consultant in vaccine compensation court, USA.

Ова студија је показала да хекса и хепта пептиди спај гликопротеина СЦ2в показују сличност са протеинима код (неких) сисара.

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На основу ове анализе следи да је молекуларна мимикрија потенцијални механизам који доприноси или узрокује СЦ2в-ом изазвано клиничко стање код људи.

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Узимајући најмању сличност секвенце СЦ2в спајк гликопротеина са протеинима примата, резултати студија које користе примате као експерименталне моделе (резус макаки) не би били поуздани јер је немогуће проверити појаву унакрсне реактивности која је повезана са аутоимунитетом, онда када не постоји сличност секвенци.

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