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Relationships between Influenza viruses A and B and Severe Acute RespiratorySyndrome-Coronavirus-2 (SARS-CoV-2): sequence homologies and implications for medicine treatment

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Abstract
In this study, we compared sequences of influenza A H1N1 and influenza B to those encoded by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with the goal of identifying homologous regions that might be exploited for the development of prophylactic or therapeuticmeasures that might be used against all three viruses. Likewise, relatively high homology suggests the possibility that individuals who experienced a severe influenza A or B infection within the past 1–2 years would have some endogenous immunity to SARS-CoV-2. While the current influenza vaccine was shown to be ineffective against SARS-CoV-2, we found that coronavirus CDS 9 encodes a protein with high homology to the nucleocapsid protein of influenza B virus; similarly, coronavirus CDS 11 encodes proteins that are homologous to surface proteins NA and NB of influenza A or B viruses, respectively. The results of this study suggest the possibility that antivirals in development or already in use for the medicinetreatment of influenza can be effective against SARS-CoV-2.
Keywords*: COVID-19, Influenza A virus, Influenza B virus, Homology, Medicine*

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I. Introduction

Japan experienced an influenza epidemic during the 2018–2019 season; in contrast, in 2019–2020, there was a substantial decline in the number of reports of influenza virus infection after the 12th week of the year (Figure 1). This finding contrasted with the number of reports ofSARS-CoV-2 infection, which increased rapidly during this period. On April 7, 2020, the Japanese government declared a state of emergency; at that time, lockdown was already underway in both Europe and in the United States.

Although the SARS-CoV-2 is a novel virus, 80% of those infected experience mild or asymptomatic disease. As such, we cannot rule out the possibility that the population at large harbors some level of pre-existing immunity due to homology between SARS-CoV-2 and an endemic virus pathogen. Likewise, use of the anti-influenza antiviral agent, Avigan (favipiravir) to coronavirus-infected patients is currently under consideration[1)] . There only a few previous papers that consider potential relationships between gene sequences of influenza viruses and those of SARS-CoV-2. Lai et al.[2)] analyzed fifty-two coronavirus genomes that were available on February 4, 2020 at Global Initiative on Sharing All influenza Data; the authors reported that the reproduction number increased from 0.8 to 2.4 since December 2019. Likewise, Yun et al.[3)] performed a retrospective analysis of nucleic acid sequence and blood test data collected from 2510 virus-infected patients; they reported that the rate of infection with influenza A and B infection was higher than that of SARS-CoV-2. Similar to our study, Chan et al.[4)] characterized coronavirus genomes across species and identified genome-wide patterns of variation encompassing different coronavirus strains; similar variations involving influenza A H1N1 virus were considered. Moreover, Anderson and Reiter[5)] reviewed the role of the melatonin-mediated signaling pathway role with respect to the pathogenesis of viral infections, with an emphasis on influenza and COVID-19; their results suggested that immune regulators might be appropriate targets in both COVID-19 and other respiratory viral infections. Likewise, Grant et al.[6)] reviewed the roles of vitamin D inreducing the risk of respiratory tract infections. However, to the best of our knowledge, there areno previous studies that examine gene sequence homologies in order to generate predictionsregarding both influenza and SARS-CoV-2 infections.As such, in this study, we examined gene sequence homologies of influenza A (A/PuertoRico/8/1934) and influenza B viruses (B/Lee/1940) with those of SARS-CoV-2 (Wuhan-Hu-1).

II. Material and Methods

The function of each genome segment of influenza A and B viruses has been identified. We used this information to guide our comparisons with the SARS-CoV-2 genome. The gene sequences of influenza A virus, influenza B virus and SARS-CoV-2 were identified using data from the National Center for Biotechnology Information (NCBI; Bethesda, MD, USA). Given their propensity to undergo mutation, the strains used for each comparison were selected in order to satisfy the following criteria:

(1) The genomic sequences of the strains selected must be as close as possible to the original prototype strain.
(2) The function of the specific genomic segments in the influenza viruses required clear and specific documentation.

In this study, the following three virus strains were selected for evaluation:

1) Influenza A virus, complete genome
   Influenza A virus (A/Puerto Rico/8/1934(H1N1))
   RefSeq: GCF_000865725.1
2) Influenza B virus, complete genome
   Influenza B virus (B/Lee/1940)
   RefSeq: GCF_000820495.2
3) SARS-CoV-2, complete genome
   Wuhan-Hu-1 isolate
   NCBI Reference Sequence: NC_045512.2

The segments' open reading frames encoded by each virus were converted into amino acids used to set protein sequence homology comparisons within the BLAST algorithms in NCBI for the following three virus pairs:

(a) Influenza A virus and influenza B virus
(b) Influenza A virus and SARS-CoV-2
(c) Influenza B virus and SARS-CoV-2

III. Results

The values calculated for homology percent as determined by NCBI Blast comparisons of the aforementioned virus sequences are summarized in Tables 1, 2, and 3. Table 4 shows the segment function of each of the three viruses, particularly SARS-CoV-2.

As shown in Table 1, many of the sequences encoded by the genome segments of influenza A and influenza B reach 100% identity, although there is segment with substantially lower sequence homology (0%–93.75%). Among these are the PB proteins (PA; PB1; and PB2) that promote virus replication and transcription from virus promoters[7,8] others include envelope proteins[7,8] and other surface constituents (NA)[7-9]. When considering all three viruses, significant homologies among individual NP, NA, and M proteins were discovered.

When comparing only the two influenza viruses, segments 4, 5, 6, and segment 7 have 100% sequence homology; however there are no significant homologies between these segments and similar coding sequences identified in SARS-CoV-2 (Tables 2 and 3). However, theSARS-CoV-2 genome coding sequences have high homology (≥80%), with the same segmentsencoded by influenza B virus (Table 4); interestingly, CDS 5 and 6 of SARS-CoV-2 have nohomology with segment 3 of influenza A. Among the hypotheses, segment 7 of influenza B andCDS 5 of SARS-CoV-2 include sequences encoding the E (envelope) protein, which is anantigen area in SARS-CoV-2[10]. As such, influenza B virus mayencode a sequence that has evolved from influenza A.

Our results also suggest that CDS 6 of SARS-CoV-2 sequence corresponding to segment 7 of influenza B virus may encode M1 protein. The CDS 5 and 6 of SARS-CoV-2 may promote functions that are similar to PA[7-9] and M1 of influenza B virus[9]. Likewise, CDS 9 of SARS-CoV-2 sequence similar to segment 5 of influenza B may function similarly to NP. Sequence homologous to CDS 11 of N which is one of antigen areas in SARS-CoV-2[11] may function similarly to NA protein encoded influenza A and B virus[7-9].

The influenza B virus genome encodes an NB protein that is not found within the genome of influenza A virus. Given our hypothesis that influenza B evolved from influenza A virus, this novel protein may have been acquired sometime after the split between these two virus strains. The NB gene encodes a protein with similarities to pathogen recognition receptors[9], although its precise function with respect to influenza B virus infection remains unclear. Likewise, the functions of influenza A proteins PA and M2 remain undefined; as such, it is perhaps not surprising to find no specific homology between sequences encoding these two influenza A proteins and genome sequence of SARS-CoV-2. With respect to development of novel antiviral medicines and/or vaccines, researchers might focus on the most highly homologous segments so as to generate an agent that will be effective against all three viruses.

IV. Discussion

Many of the most significant differences between influenza A virus, influenza B virus and SARS-CoV-2 relate to the distinct sequences encoding the M1[7,8)] and the NP[7-9)] proteins. In this study, we identified sequence homologies among proteins encoded by the influenza A virus, influenza B virus, and SARS-CoV-2; putative functions for four of the 12 CDSs of the SARS-CoV-2 genome were revealed. Furthermore, the relative high homology among these sequences suggests the possibility that individuals who experienced infections with either influenza A or influenza B within 1–2 years might have mild or no symptoms of COVID-19. An epidemiological survey directed specifically at this hypothesis might be undertaken in the near future.

While the influenza vaccine does not provide effective protection against COVID-19, the resultsof this study suggest that one or more of the antivirals in use or in development to combatinfluenza infection might be examined for use against SARS-CoV-2 infection. Coronavirus iscurrently fractionated into twelve CDSs; these contain both short and long, as well asoverlapping coding sequences. Therefore, it is necessary to review the individual segments so asto verify function as information becomes available.

V. Conclusions

The genome of the coronavirus pathogen, SARS-CoV-2, includes four regions that display highhomology (80 % or more) with genome segments that are unique to influenza B virus. As such,this study may be among the first to consider the possibility that antivirals directed againstinfluenza might be effective for the treatment COVID-19. Notably, this homology involvesCDSs 5, 6, 9, and 11 of SARS-CoV-2. Currently, SARS-CoV-2 is fractionated into twelvedistinct CDSs; ongoing review of these designations will be necessary as progress in this fieldelucidates structure and function, that latter of which will need to undergo functionalverification.

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Declarations interest

None.

Author Contribution

Makiko TAKECHI: Project administration, Conceptualization, Data curation, Investigation, -Methodology, Resources, Software, Supervision, Validation. Shinya NAGASAKI: Administration, Data curation, Investigation, Resources, Supervision, review & editing. Kibo NAGASAKI: Investigation; Visualization.

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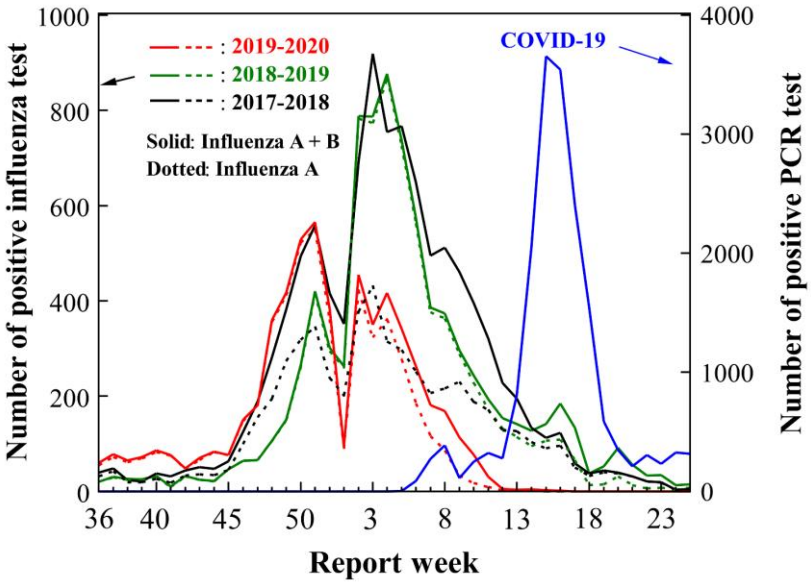

Figure 1

Seasonal variation in the numbers of positive tests for influenza virus and the number ofpositive PCR tests for SARS-CoV-2 in Japan. The red, green and black lines represent thenumber of positive tests for influenza in 2019–2020, 2018–2019 and 2017–2018, respectively.The solid and dotted lines represent total number of positive tests for influenza A and B, andinfluenza A only, respectively. The blue line represents the number of positive PCR tests forSARS-CoV-2. Report week 1 corresponds to December 30, 2019 to January 5, 2020 in 2019–2020, December 31, 2018 to January 6, 2019 in 2018–2019, and January 1, 2018 to January 7,2018 in 2017–2018.

Table 1

Homology (%) between proteins encoded by segments of the RNA genomes of influenza A H1N1 (A/Puerto Rico/8/1934) and influenza B virus (B/Lee/1940); S, segment number.

		Influenza B virus							
		RNA 1	S 2	S 3	S 4	S 5	S 6	S 7	S 8
Influenza A virus	S 1	0.00	0.00	100.00	100.00	100.00	100.00	100.00	100.00
	S 2	84.71	100.00	100.00	100.00	100.00	100.00	90.48	100.00
	S 3	100.00	100.00	72.27	100.00	100.00	100.00	90.48	100.00
	S 4	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
	S 5	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
	S 6	100.00	0.00	0.00	100.00	100.00	100.00	100.00	0.00
	S 7	100.00	100.00	93.75	100.00	100.00	93.75	100.00	0.00
	S 8	100.00	100.00	100.00	100.00	100.00	0.00	100.00	0.00

Table 2

Homology (%) between proteins encoded by segments of the RNA genome of influenza A H1N1 (A/Puerto Rico/8/1934) and proteins encoded bythe genome of the SARS-CoV-2 Wuhan-Hu-1 isolate. The function of each genome segment and coding sequence (CDS) are as shown.

CDS No.and function / Segment No.and function		1	2	3	4	5	6	7	8	9	10	11	12
		ORF1ab	unkown	S	ORF3a	E	M	ORF6	ORF7a	ORF7b	ORF8	N	ORF10
S1	PB2[1.2)] PB1-F2	26.67	26.67	36.36	29.41	0.00	38.46	0.00	29.41	0.00	0.00	35.71	30.43
S2	PB1[2)]	21.47	21.23	40.00	31.82	31.25	57.14	33.33	60.00	0.00	57.14	50.00	33.33
S3	PA[1.2)] PA-X	26.47	28.00	33.33	50.00	0.00	0.00	0.00	50.00	0.00	23.08	35.71	0.00
S4	HA[1.2.3)]	40.00	40.00	35.00	25.00	29.41	54.55	18.52	0.00	60.00	26.09	33.33	0.00
S5	NP[1.2.3)]	19.25	37.93	38.10	21.88	0.00	36.36	0.00	0.00	66.67	0.00	28.57	36.36
S6	NA[1.2.3)]	24.44	27.91	27.78	22.22	23.08	43.75	33.33	30.00	0.00	23.33	30.88	42.11
S7	M2[3)] M1[3)]	50.00	21.88	28.95	33.33	0.00	27.27	42.86	0.00	0.00	0.00	0.00	0.00
S8	NEP[3)] NS1[2.3)]	21.82	21.82	40.00	21.43	0.00	0.00	0.00	26.67	0.00	19.23	30.77	0.00

Table 3

Homology (%) between proteins encoded by segments of the RNA genome influenza B virus (B/Lee/1940) and proteins encoded by the genome ofthe SARS-CoV-2 Wuhan-Hu-1 isolate. The function of each genome segment and coding sequence (CDS) are as shown.

CDS No.and function / Segment No.and function		1	2	3	4	5	6	7	8	9	10	11	12
		ORF1ab	unkown	S	ORF3a	E	M	ORF6	ORF7a	ORF7b	ORF8	N	ORF10
RNA1	PB1[2)]	27.27	26.97	36.00	18.52	31.25	43.33	57.14	28.12	0.00	0.00	50.00	0.00
S2	PB2[1.2)]	23.71	23.71	0.00	41.67	66.67	54.55	50.00	33.33	0.00	35.71	36.36	0.00
S3	PA[1.2)]	27.69	39.13	54.55	41.67	80.00	83.33	0.00	0.00	0.00	18.60	60.00	54.55
S4	HA[1.2.3)]	34.38	34.38	37.14	39.13	36.84	33.33	46.67	26.09	0.00	36.36	25.00	0.00
S5	NP[1.2.3)]	36.36	25.93	28.57	41.67	0.00	31.58	0.00	0.00	80.00	26.76	28.57	0.00
S6	NB[3)] NA[1.2.3)]	36.59	36.59	22.56	26.39	37.50	0.00	0.00	25.00	0.00	0.00	85.71	36.36
S7	M1[1.2)]	54.55	30.00	26.32	0.00	80.00	83.33	0.00	33.33	0.00	0.00	30.43	21.05
S8	NEP[3)] NS1[3)]	28.57	28.57	54.55	0.00	40.00	0.00	37.50	57.14	0.00	0.00	0.00	0.00

Table 4

Combinations of segments and encoded proteins that display high homology (≥80%) betweeninfluenza A H1N1 (A/Puerto Rico/8/1934) or influenza B virus (B/Lee/1940) and proteinsencoded by the SARS-CoV-2 Wuhan-Hu-1 isolate. Values in the table represent homologies between influenza A H1N1 and SARS-CoV-2 / homologies between influenza B and SARS-CoV-2. The areas where the three viruses have common proteins are shown in gray.

Segment (no. and function)of Inf A H1N1 and Inf B / CDS (no. and function) of SARS-CoV-2		S3	S5	S6	S7
		PA, PA-X	NP	NA	M1, M2
		PA	NP	NB, NA	M1
S5	E	0.00/80.00	-	-	0.00/80.00
S6	M	0.00/83.33	-	-	27.27/83.33
S9	ORF7b	-	66.67/80.00	-	-
S11	N	-	-	30.88/85.71	-

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