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Letter

Mimicry between proteins of human and avian influenza viruses and host immune system proteins

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Abstract: Viral infection can lead to dangerous and severe manifestations associated with immunosuppression and a cytokine storm. The last is typical for influenza A virus infection of H1N1 subtype, when the level of cytokines in the peripheral blood is significantly elevated, leading to severe inflammatory damage and pathogenesis. In the present study, we performed a comparative computer analysis of amino acid fragments of host immune system proteins homologous to amino acids fragments of viral proteins of influenza A viruses of H1N1 subtype and avian influenza viruses of H5N1 and H7N9 subtypes. Homologous amino acid sequences of cellular protein integrin-α L and NALP1 were found in PB2 proteins of all studied viruses, as well TNF-α—in NP proteins. In addition, amino acid sequences homologous in IL-36 to NA proteins and C9 in M1 in H1N1 and H5N1 subtypes were found. At the same time, avian influenza viruses significantly differ from human influenza viruses in the composition of mimicking cellular proteins. In particular, avian influenza viruses have fragments homologous to different proteins of the NALP family (3, 13), TLR, IL-13, CD22, CD55, that are absent in human influenza A (H1N1)pdm09 viruses. Bioinformatic analysis data on the detection of fragments in the structure of influenza virus proteins that mimic the proteins of the innate and adaptive human immune system will serve as the basis for experimental studies to identify the role of homologous fragments in the regulation of the host immune system.

Keywords: viral proteins; host immune proteins; primary structure of proteins

1. Introduction

Infection of host cells with a virus leads to the activation of its immune system (both innate and adaptive), the main defense system aimed at eliminating the pathogen. Each virus has its own set of mechanisms to "overcome" the host immune system, deactivating its innate and adaptive subsystems by modulating more than 300 cellular proteins of the host immune system, not counting the modulation of miRNA [1–11]. The products of viral genome transcription and replication, as well as viral proteins, can act as triggers for pathological reactions. Especially dangerous and severe manifestations of a viral infection are associated with immunosuppression and cytokine storm. The last is especially characteristic in influenza A virus infection caused by subtype (H1N1)pdm09, where the level of cytokines in the peripheral blood exceeds their normal concentration by tens or more times, which leads to development of a severe clinical picture [12–14]. However, the mechanisms of the development of immunosuppression in influenza infection are not fully understood.

The aim of the study was to identify, using computer analysis in the proteins of human and avian influenza viruses, amino acid sequences homologous to the amino acid sequences of the main components of the human immune system, for further study of the mechanisms to "overcome" the host immune system by influenza viruses.

2. Materials and methods

2.1. Viruses

The following viruses were used for comparative computer analysis: human and avian influenza A viruses: A/California/04/2009 H1N1(pdm09), A/California/66/2017 H1N1(pdm09), A/Chicken/Hubei/Wh/1997 (H5N1), A/Anhui/1/2013 (H7N9). The virus strains selection was dictated by the presence on the Internet of a database of primary structure of respiratory virus proteins.

2.2. Primary structure of immune system proteins and the studied virus proteins

All protein sequences were used from databases available on the internet (www.ncbi.nlm.nih.gov, www.nextprot.org, www.viralzone.expasy.org). The peptides of 12 amino acids in length were considered as homologous if they had 7 and more identical positions.

The article uses the international amino acid code: alanine (A), cysteine (C), aspartic acid (D), glutamic acid (E), phenylalanine (F), glycine (G), histidine (H), isoleucine (I), lysine (K), leucine (L), methionine (M), asparagine (N), proline (P), glutamine (Q), arginine (R), serine (S), threonine (T), valine (V), tryptophan (W), tyrosine (Y).

For comparative computer analysis, about 70 basic cellular proteins of the innate and adaptive human immune system with known primary structures were selected, including INFs, ILs, TNF-α, RIG-1, integrins, system complement proteins, CD molecules in B- and T- lymphocytes and others. For human and avian influenza viruses, both structural proteins (HA, PB1, PB2, HA, NA, NP, M1, M2) and non-structural (NS1, NS2) were analyzed.

All protein sequences were used from databases available on the internet

(www.ncbi.nlm.nih.gov; www.nextprot.org; www.viralzone.expasy.org). The search for homologous fragments in the structure of viral proteins and host immune system proteins was carried out by comparing fragments of 12 amino acids in length, which were assigned as homologous with identity in ≥8 positions.

3. Results

Table 1 represents the results of a comparative analysis of primary structure of influenza A (H1N1)pdm09 viruses, H5N1 and H7N9 proteins with the structure of a different host immune system proteins.

Table 1. Pairs of homologous fragments in some host immune system proteins and proteins of influenza viruses A (H1N1)pdm09 isolated in 2009 and 2017, H5N1 and H7N9 isolated in 1997 and 2013.

Homologous fragments in viral and host immune system proteins	Amino acid sequence alignment of influenza virus A/California/04/2009 H1N1(pdm09) proteins	Amino acid sequence alignment of influenza virus A/California/66/2017 H1N1(pdm09) proteins
PB2 (638–649)*	V N V R G S G L R I L V	V N V R G S G L R I L V
CD7 (120–131)**	| | | | | | | : | |	| | | | | | : | |
	V N V Y G S G T L V L V	V N V Y G S G T L V L V
PB2 (417–428)*	D L N F V N R A N Q R L	D L N F V N R A N Q R L
NALP 1 (856–867)**	| | : | | | | | | |	| | : | | | | | | |
	D L A F G L R A N Q T L	D L A F G L R A N Q T L
PB2 (512–523)*	L L S P E E V S E T Q G	L L S P E E V S E T Q G
Integrin α-L (501–512)**	| : | | | | | | |	| : | | | | | | |
	Q L G F E E V S E L Q G	Q L G F E E V S E L Q G
PA (683–694)*	L G G L Y E A I E E C L	L G G L Y E A I E E C L
NALP7 (572–583)**	| | | | | : | | | |	| | | | | : | | |
	L G C L Y E S Q E E E L	L G C L Y E S Q E E E L
PA (63–74)*	V E S G D P N A L L K H	V E S G D P N A L L K H
Integrin α-L (212–223)**	| : : | | | | | | |	| : : | | | | | | |
	V K R K D P D A L L K H	V K R K D P D A L L K H
PA (268–281)*	P D G P L C H Q R S K	P D G P L C H Q R S K
TNF-α (551–564)**	: | | | | | | | |	: | | | | | | | |
	S L P P S C H Q R S K	S L P P S C H Q R S K
PA (682–695)*	D L G G L Y E A I E E C	D L G G L Y E A I E E C
TNF-α (429–442)**	| | | | | : | | |	| | | | | : | | |
	D L L G C L E D I E E A	D L L G C L E D I E E A
HA (537–548)*	V A S S L V L V V S L G	V A S S L V L V V S L G
CD8 β (177–188)**	| | : | | | : | | |	| | : | | | : | | |
	V A G V L V L L V S L G	V A G V L V L L V S L G

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Homologous fragments in viral and host immune system proteins	Amino acid sequence alignment of influenza virus A/California/04/2009 H1N1(pdm09) proteins												Amino acid sequence alignment of influenza virus A/California/66/2017 H1N1(pdm09) proteins											
HA (221–232)*	S	R	Y	S	K	K	F	K	P	E	I	A	S	R	Y	S	K	K	F	K	P	E	I	A
RIG-I (465–476)**	|	|		|	:	|	|	|		|	|		|	|		|	:	|	|	|		|	|
	S	R	I	S	D	K	F	K	Y	I	I	A	S	R	I	S	D	K	F	K	Y	I	I	A
NA (168–179)*	S	P	Y	N	S	R	F	E	S	V	A	W	S	P	Y	N	S	R	F	E	S	V	A	W
IL-36 (112–123)**	|			|	|		|	|	|	|	|			|	|		|	|	|	|	|	
	S	G	R	N	S	T	F	E	S	V	A	F	S	G	R	N	S	T	F	E	S	V	A	F
NA (168–179)*	I	S	F	C	G	V	D	S	D	T	V	G	I	S	F	C	G	V	D	S	D	T	V	G
TNF-α (112–123)**	|	|		|	:	|	|		|	|	|		|	|		|	:	|	|		|	|	
	I	S	S	C	T	V	D	R	D	T	V	C	I	S	S	C	T	V	D	R	D	T	V	C
NP (89–100)*	P	K	K	T	G	G	P	I	Y	R	R	V	P	K	K	T	G	G	P	I	Y	R	R	V
TNF-α (18–29)**	|	|	|	|	|	|	|				|		|	|	|	|	|	|				|	
	P	K	K	T	G	G	P	Q	G	S	R	R	P	K	K	T	G	G	P	Q	G	S	R	R
M1 (110–121)*	H	G	A	K	E	V	S	L	S	Y	S	T	H	G	A	K	E	V	S	L	S	Y	S	T
CD2 (339–350)**	|	|	|		|		|	|	|		| :	|	|	|		|		|	|	|		|	:
	H	G	A	A	E	N	S	L	S	P	S	S	H	G	A	A	E	N	S	L	S	P	S	S
M1 (110–121)*	T	I	G	T	H	P	S	S	S	A	G	L	T	I	G	T	H	P	S	S	S	A	G	L
C9 (339–350)**	|		|	|	|		|	|	|	:	:	|	|		|		|	|	|		:	:	|
	T	Y	G	T	H	Y	S	S	S	G	S	L	T	Y	G	T	H	Y	S	S	S	G	S	L
M1 (20–31)*	L	K	A	E	I	A	Q	R	L	E	S		L	K	A	E	I	A	Q	R	L	E	S	
NALP9 (518–530)**	|	|	:	|	|	:	|		|	|	|		|	|	:	|	|	:	|		|	|	|	
	L	K	Q	E	I	T	Q	C	L	E	S		L	K	Q	E	I	T	Q	C	L	E	S	
NS2 (19–30)*	Q	L	G	S	S	S	E	D	L	N	G		Q	L	G	S	S	S	E	D	L	N	G	
CD72 (148–159)**	|	|	|		|	:	|	|	|	:	|		|	|		|	:	|	|	|	:	|	
	Q	L	G	Q	S	A	E	D	L	Q	G		Q	L	G	Q	S	A	E	D	L	Q	G	

Homologous fragments in viral and host immune system proteins	Amino acid sequence alignment of influenza virus A/Chicken/Hubei/Wh/1997 (H5N1) proteins												Amino acid sequence alignment of influenza virus A/Anhui/1/2013 (H7N9) proteins											
PB2 (638–649)*	V	N	V	R	G	S	G	L	R	I	L	V												
CD7 (120–131)**	|	|	|		|	|	|			:	|	|											
	V	N	V	Y	G	S	G	T	L	V	L	V												
PB2 (417–428)*	D	L	N	F	V	N	R	A	N	Q	R	L	D	L	N	F	V	N	R	A	N	Q	R	L
NALP 1 (856–867)**	|	|	:	|			|	|	|	|		|	|	|	:	|			|	|	|	|		|
	D	L	A	F	G	L	R	A	N	Q	T	L	D	L	A	F	G	L	R	A	N	Q	T	L
PB2 (512–523)*	L	L	S	P	E	E	V	S	E	T	Q	G	L	L	S	P	E	E	V	S	E	T	Q	G
Integrin α-L (501–512)**		|	:		|	|	|	|	|		|	|		:		|	|	|	|	|		|	|
	Q	L	G	F	E	E	V	S	E	L	Q	G	Q	L	G	F	E	E	V	S	E	L	Q	G
PB2 (684–695)*	A	G	V	E	S	A	V	L	R	G	F	L	A	G	V	E	S	A	V	L	R	G	F	L
VLA-3 α (500–511)**	|	|		|	|	|	|	:	:	|	|	:	|	|		|	|	|	|	:	:	|	|
	A	G	S	E	S	A	V	F	H	G	F	F	A	G	S	E	S	A	V	F	H	G	F	H

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Homologous fragments in viral and host immune system proteins	Amino acid sequence alignment of influenza virus A/Chicken/Hubei/Wh/1997 (H5N1) proteins	Amino acid sequence alignment of influenza virus A/Anhui/1/2013 (H7N9) proteins
PB2 (625–636)*		P P K Q S R M Q F S S L
IL-13 (105–116)**		| : | | : | | | | |
		P H K V S A G Q F S S L
PB2 (558–549)*		E N V K I Q W S Q D P T
NALP 13 (107–118)**		| | | : | | | | | |
		E N V Q T Q E L Q D P T
PA (683–694)*	L G G L Y E A I E E C L	
NALP 7 (572–583)**	| | | | | : | | |	
	L G C L Y E S Q E E E L	
PA (63–74)*	V E S G D P N A L L K H	
Integrin α-L (212–223)**	| : : | | : | | | |	
	V K R K D P D A L L K H	
HA (329–340)*; (27–38)*	L A T G L R N T P Q R E	A V S N G T K V N T L T
TNF-α (404–415)**;	| | | | : | | : | |	| | | | | | | | :
(160–171)**	L A T W R R R T P R R E	A V S Y Q T K V N L L S
HA (536–547)*		I L L A I V M G L V F I
TNFR1 (204–215)**		| | : | | : : | | | |
		I L F A I L L V L V F I
HA (457–468)*		L Y E R V K R Q L R E N
TLR2 (334–345)**		| | | | | | | | |
		L T E R V K R I T V E N
HA (206–217)*		S G N K L V T V G S S N
TLR10 (411–422)**		| | | | | | | : : |
		S G N K L V T L P K I N
NA (168–179)*	S P Y N S R F E S V A W	
IL-36 (112–123)**	| | | | | | | |	
	S G R N S T F E S V A F	
NA (247–258)*		A D T R I Y Y F K E G K
CD80 (60–71)**		| : | | | | : | | |
		A Q T R I Y W Q K E K K
NP (89–100)*	P K K T G G P I Y R R V	P K K T G G P I Y R R V
TNF-α (18–29)**	| | | | | | | | : |	| | | | | | | | : |
	P K K T G G P Q G S R R	P K K T G G P Q G S R R
NP (45–53)*		Q M C T E L K L S D N E
NALP3 (741–752)**		| | | | | : | | | | :
		Q S L T E L D L S D N S
M1 (218–229)*	T I G T H P S S S A G L	
C9 (341–352)**	| | | | | | | : : |	
	T Y G T H Y S S S G S L	

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Homologous fragments in viral and host immune system proteins	Amino acid sequence alignment of influenza virus A/Chicken/Hubei/Wh/1997 (H5N1) proteins	Amino acid sequence alignment of influenza virus A/Anhui/1/2013 (H7N9) proteins
NS1 (73–84)*	S D E A L K M T I A S V	
Igk (13–24)**	| | | : | | : : | | |	
	S D E Q L K S G T A S V	
NS1 (205–216)*		S S D E D G R S P L S T
CD22 (663–674)**		| | | | | | | | | |
		N S V G K G R S P L S T
NS2 (20–31)*	Q L G S S S E D L N G	
CD72 (149–160)**	| | | | : | | | : |	
	Q L G Q S A E D L Q G	
NS2 (20–31)*	M R M G D L H S L Q S R	M R M G D L H S L Q S R
CD55 (149–160)**	| | | | | | | | | |	| | | | | | | | | |
	M R W C D R S S L Q S R	M R W C D R S S L Q S R

Note: "|" = identical amino acids; ":" = isofunctional amino acids; "*" = amino acid sequence of a protein fragment of influenza virus; "**" = amino acid sequence of a fragment of host immune system protein.

As shown in Table 1, in the structure of almost all proteins of the studied influenza viruses were found amino acid sequences homologous to the amino acid sequences of host immune system proteins with a high degree of homology, with the exception of PB2, M2 and NS1 proteins. Thus, fragments homologous to integrin α-L were found in the PB2 and PA proteins of the studied influenza viruses, but these fragments differed in localization in the integrin molecule. Viral proteins PB2, PA, and M1 contain fragments of amino acids homologous to family of cytoplasmic cellular proteins involved in activation of caspase-1 (NALP)—NALP1, NALP7 and NALP9. Viral proteins PA, NA and NP contain amino acid fragments that are homologous to different fragments of tumor necrosis factor protein (TNF-α). Moreover, in PA protein of 2 studied influenza A (H1N1)pdm09 viruses were found 2 homologous fragments to TNF-α. In addition to the mimicry of the above-mentioned cellular proteins, in proteins of each virus strain was revealed a number of specific amino acid sequences homologous to cellular proteins: CD7 (T-cell co-receptor) in the PB2 structure; CD8 (T-cell co-receptor) and RIG1 (receptor of gene 1 induced by retinoic acid) in HA; IL-36 in NA; CD2 (T-cell surface antigen) and C9 (complement system protein) in M1; CD72 (B-cells co-receptor) in NS2. There was no difference in composition and location of amino acid sequences of 2 investigated influenza A viruses homologous to host immune system proteins.

In protein structure of avian influenza viruses H5N1 and H7N9, amino acid sequences homologous to the amino acid sequences of host immune system proteins were also identified. Homologous fragments of avian influenza virus were localized in the viral proteins PB2, PA, HA, NA, NP, M1, NS1, NS2, with the exception of the PA protein in the H7N9 avian influenza virus. Identical homologous fragments were identified in the proteins of influenza viruses H5N1 and H7N9 and cellular proteins such as integrins-α, NALP1, VLA-3 α (very late antigen-3) in PB2, TNF-α in NP, CD55 in NS2. At the same time, there were also significant difference between these viruses in the mimicry of host immune system proteins. Thus, in the structure of the PB2 protein of the H7N9 virus, two fragments homologous to IL-13 and NALP13 were found, which were absent in the structure of the same protein of the H5N1 virus, and a fragment homologous to CD7 present in

H5N1 was absent. In the structure of the PA of the H7N9 virus, no homologous fragments were found, while in the same protein of the H5N1 virus there are fragments homologous to integrin-α and NALP7. In structure of HA protein of the H7N9 virus, 4 fragments homologous to TNF-α, the TNF-α receptor, TLR2 (toll-like receptor 2) and TLR10 were identified, whereas in the HA of the H5N1 virus only one fragment, homologous to TNF-α, different from the H5N1 virus; NA protein of the H7N9 influenza virus contained one fragment homologous to CD80, and NA of the H5N1 influenza virus to IL-36; NP protein of H7N9 differed from H5N1 only in one fragment homologous to NALP3. Structure of the M1 protein of the H7N9 virus has one fragment homologous to NALP7, and the M1 protein of the H5N1 virus to C9. NS1 protein of the H7N9 virus contained fragment homologous to Igk, and NS1 of the H5N1 virus to CD22; NS2 protein of the H5N1 and H7N9 viruses differed only in one fragment, which was homologous to CD72 in H5N1 virus.

Thus, comparison of fragments homologous to proteins of the immune system, in proteins of avian influenza viruses (H5N1 and H7N9), showed both common fragments homologous to cellular proteins and fragments characteristic of each studied virus.

Comparing fragments mimicking the cellular proteins of host immune system in the proteins of human influenza viruses A (H1N1)pdm09 and avian influenza viruses (H5N1 and H7N9), showed that identical amino acid sequences were found with integrins-α and NALP1 in PB2 proteins, as well as with TNF-α in NP proteins. In addition, common homologous amino acid sequences were found in the NA proteins with IL-36 and M1 with C9 in the H1N1 and H5N1 viruses. At the same time, avian influenza viruses differ significantly from human influenza viruses in the composition of mimicking cellular proteins, in particular, avian influenza viruses have fragments homologous to different proteins of the NALP family (-3, -13), TLR, IL-13, CD22, CD55, absent in human influenza A (H1N1)pdm09 viruses.

4. Discussion

A comparative analysis the primary structure of the basic proteins of the innate and adaptive human immune system, with the primary structure of the viral proteins of influenza showed that all studied proteins of human and avian influenza viruses are characterized by the presence of homologous sequences to such proteins of host immune system as complement system proteins, integrins, inhibitor of apoptosis proteins, interleukins, toll-like receptors and others (Table 1). It is interesting to note that the largest number of homologous sequences is concentrated mainly in viral proteins with polymerase activity, such as PA and PB2 (human influenza A (H1N1)pdm09 virus), PA and PB2 (avian influenza viruses H5N1) and PB2 (avian influenza viruses H7N9) (Table 1). In other viral proteins (envelope, internal and non-structural), amino acid fragments homologous to the cellular proteins of host immune system were also found, but the number of fragments were smaller (from 1 to 4 fragments).

What role can mimicry of cellular proteins in viruses play in the regulation of the host immune system? Pathological conditions, especially infections, are characterized by violations of excretory processes and accumulation of cellular degradation products due to an imbalance between processes of synthesis and metabolism. Therefore, it is quite likely that fragments of viral proteins homologous to the immune system proteins, disorganize the immune system, being released during proteolysis of viral proteins. The cleavage of mimic fragments from viral proteins can occur due to either cellular or viral proteases. In many viruses, proteases are programmed in their genome, in addition, structural

viral proteins may also have protease activity. This assumption is confirmed by detection of the protease activity of the PA polymerase protein in the influenza virus [15]. The mechanism for the release of active peptides by proteolysis of precursor proteins is widely known in biochemistry, and it is in this way that regulatory peptides are synthesized that are involved in many body processes. For example, it is an established fact that the VIP peptide is released as a result of proteolysis of a protein with a molecular weight of 17500 in the form of a fragment of about 25 aa. This peptide, along with other functions, takes an active part in the activation of the host's adaptive and innate immunity. Suppression of the activity of this peptide leads to the development of immunosuppression.

Another potential mechanism of dysregulation may be manifested in the induction of an immune response to homologous fragments of viral proteins, in particular, antibody formation to them that are also capable of recognizing and blocking, respectively, those host proteins that contain those homologous fragments. The possibility of such a variant of the pathogenesis of autoimmunity is confirmed by the results of vaccination against the 2009–2010 influenza pandemic. Vaccination with the Pandemrix vaccine (GlaxoSmithKline) has resulted in a sharp increase in the incidence of narcolepsy in children and adolescents in different countries. Comparison of the characteristics of different vaccines showed the existence of a connection between the occurrence of narcolepsy and the high content of the influenza virus nucleoprotein in the pandemrix vaccine and antibody formation to it that cross-reacted with the hypocretin (orexin) receptor 2. As it turned out, the hypocretin 2 receptor contains a motif in its extracellular loop, presented also in nucleoprotein [16–19].

5. Conclusions

Bioinformatic analysis data on the detection of fragments in the structure of influenza virus proteins that mimic the proteins of the innate and adaptive human immune system will serve as the basis for experimental studies to identify the role of homologous fragments in the regulation of the host immune system.

Conflict of interest

All authors declare no conflicts of interest in this paper.

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