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GENERAL CHARACTERISTICS OF INFLUENZA VIRUS A MOLECULAR STRUCTURE

Abstract. The influenza virus is one of the most abundant viruses in the world. It causes both mild seasonal infections and severe pandemics killing thousands of people and mammals. Two main extracellular receptors – neuraminidase (NA) and hemagglutinin (HA) are responsible for infection symptoms development and spread. Error-prone RNA-polymerase incorporates mutations into both neuraminidase and hemagglutinin per replication cycle, which complicates the development of highly effective drugs against animal influenza. Incorporated mutations are also involved in the transition of influenza from animal to human species and vice versa. Transited influenza subtypes are the most dangerous, because it is unpredictable now, where the mutation might arise. However, it starts to become clear, which molecular regions are the most common for the mutation to occur.

This article revises the molecular structure of influenza extracellular receptors, including critical regions of receptors binding sites and susceptible mutation sites. The clear understanding of molecular structures and critical regions of HA and NA might facilitate the development of an effective vaccine and/or drug development.

Key words: influenza, neuraminidase, hemagglutinin, mutation, sialidase, virus.

INTRODUCTION. General description of influenza viruses. Influenza A viruses belong to a viral family of *Orthomyxoviridae*, what can be interpreted from Greek language as viruses which bind to mucoproteins. Influenza A viruses cause flu in many representatives of animal species, the most common hosts are: salmon, pigeon, poultry, fowl, especially chicken, swine, camel, bats and human. It should be considered that an avian virus does not cause such a wide range of symptoms in birds but as it is transmitted to humans, disease conditions might be very severe [1].

There are several types of influenza viruses: A, B and C types. Influenza A is the most studied and common type: has a wide range of hosts including mammals, fish and birds and is responsible for most flu epi- and pandemics. Influenza B virus infects only humans, and influenza C infects both human and swine [1, 2].

Influenza A virus causes a wide range of non-specific symptoms: high fever, sore throat, mild headache, chills, malaise, cough and muscular pain. These symptoms do not necessarily indicate that a person has flu. Otherwise, additional analyses should be certainly made to ensure a final diagnosis. Most harm done by influenza is towards infants and elders due to their suppressed or non-developed immune system. Sometimes it could be even fatal due to chronic illness or lack of special medical care and medicine. However, as vaccines and drugs are being improved, those fatal cases are getting much lower than in previous century [1].

There were several pandemics caused by initially swine or avian flu through the development of their transmittance to humans. It is uncommon that once in the future another pandemic virus would arise leading to enormous problems including lack of effective vaccine, inefficiency of available drugs, and may be financial losses. It is very hard to predict next pandemics and subtype of virus involved in particular, so detailed studies of viral subtypes might be a solution to overcome next potential pandemics.

Molecules mostly involved in the development of influenza infections are envelope proteins: hemagglutinin (HA) and neuraminidase (NA). Most of the drugs against flu use HA or NA as their main targets through reducing their affinity to sialic acid, destroying covalent inter- and intramolecular bonding or by using antagonistic features. For example, zanamivir and oseltamivir are NA-inhibiting drugs [1].

So, in this review we would consider molecular structure, functions and subtypes of envelope glycoproteins HA and NA, discuss interactions between viral and host molecules and briefly mention how the transition from avian to human flu is established, which is the main cause of unexpected pandemics [1].

Hosts of influenza A virus. Influenza A virus has a variety of hosts. Well known examples are chicken, domesticated birds, swine, camels, horses, bats and humans.

There is a great variety of bird species susceptible to influenza A virus: ducks, wigeons, teals, mergansers, geese, swans, redshanks, gulls, grebes and etc. Most of the avian hosts are waterfowl and only several are terrestrial such as pigeons and chicken. The most known birds infecting influenza A subtypes are highly pathogenic H5N1 initially identified in Hong Kong, H7N3 outbreak in England and Australia in 1963 and 1992-1994 respectively, H7N7 several outbreaks in Germany, England, Australia and Netherlands and H5N2 with outbreaks in USA, Mexico, Italy and China.

Swine influenza is another major source of virus reservoir in wild environment. Outbreaks of swine influenza were firstly identified in Spanish influenza pandemic in 1918 year and had occurred several times after that. Major swine influenza subtypes: H1N1, H1N2 and H3N2 [3].

Equine influenza was described as a disease having similar symptoms as human influenza since Romanian times. It has potentially evolved together with human influenza virus due to their living in close proximity with horses, mules and donkeys. Influenza virus is still considered as the most important respiratory pathogen in horse and related species. The first isolate of equine influenza was obtained in Eastern Europe in 1956 year and identified as H7N7 subtype. Another example of horse influenza is H3N8, which was isolated in 1963 and since those times is considered as enzootic in Europe and America [3].

Recently two novel influenza viral subtypes from bat species were identified and studied– H17N10 and H18N11. However, they are considered as influenza-like viruses, because their characteristics are rather distinct: a different binding site to sialic acid receptors and neuraminidase not being a sialidase [4].

However, human infecting influenza subtypes have emerged from animal infecting subtypes through the adaptation to the surroundings and incorporation of mutations per replication cycle. So, wild subtypes of influenza virus should be thoroughly studied to prepare and possibly prevent next pandemics.

General description of influenza A virus. Influenza virions have roughly spherical or filamentous shape. Newly synthesized ones have more filamentousvirions, and as they become mature, shape becomes roughly spherical. Gene segments are wrapped into helical nucleocapsid, which is then packaged into lipid envelope mostly derived from a host's plasma membrane.

Influenza A viruses are encoded by six-eight strains of negative-sense RNA. RNAs are error-prone due to RNA-dependent RNA-polymerase, which drives rapid adaption and evolution of influenza [5]. Each of the genome segments encodes one or two proteins, functions of proteins encoded together on one gene segmentare rather similar. Envelope glycoproteins, which are located on the outermost layer, HA and NA are encoded by genome segments 4 and 6, respectively [1]**.** Three RNA polymerase proteins (PA, PB1 and PB2) are encoded by distinct genome segments from 1st to 3rd. 7thgene segment codes for an integral membrane protein (M1) with ion channel activity and an envelope protein by subsequent splicing of mRNA. Influenza A virus expresses 11 proteins in total, and 9 of them are packaged into new virions. Two proteins, which are not packaged, facilitate assembly of viral particles.

Only in case all RNA gene segments are packaged into a viral particle, the virus is capable of survival and infection [5].

Influenza A virus replicates in the host nucleus, unlike most other RNA viruses such as bynuaviruses, paramyxoviruses and rhabdoviruses replicating in the cytoplasm. Viral mRNA of influenza stealscapped 5'ends of cellular mRNA in the nucleus, which facilitates rapid synthesis of new virion particles. Rapid evolution of these viruses is due to the presence of both error-prone RNA-polymerase and frequentreassortment (antigenic shift) of whole genome segments or some parts between related strains. This reassortment is the one most responsible of pandemics due to mutated surface antigens NA and HA [1].

Influenza A viruses are classified according to NA and HA subtypes, which together show different antigenic reactivity to poly- and monoclonal antibodies and show different nucleotide sequences [6].

The main difference between avian and human adapted viruses is their preferential binding to sialylated glycan receptors, hemagglutinin in particular. Human viral hemagglutinin exemplified by H1N1, H2N2, H3N2 subtypes preferentially binds to long α2-6 sialylated glycan receptors, which are mostly expressed in human upper respiratory epithelium. HA of avian influenza exemplified by H1N8, H2N9, H3N2, H3N8, H5N8 binds to short α2-3 sialylatedglycans. Due to this feature, there are only several avian influenza viruses capable tocause diseases in humansuch as H5N1, H7N7, H7N3, H9N2 serotypes. Differences in receptor specificity of human and avian influenza A viruses are also considered as features responsible for tissue tropism, host species barrier and interspecies transmission blocking. So, there is a need to constantly monitor these avian viruses to be able to detect changes in external glycan structure as they play the most important role in influenza evolution [6].

Swine influenza viruses are able to bind sialic acid in both α2-3 and α2-6 linkages, so they combine features of both human and avian viruses.

HA and NA both recognize sialylated receptors on the outside of a host cell membrane. Influenza infection is promoted by multiple HA binding to sialic acids found on the carbohydrate side chains outside regions: on surface glycoproteins and glycolipids. NA's primary function is to release accidentally bound newly synthesized HA from sialylated glycoproteins and glycolipids, however it performs other functions as well.

Neuraminidase. NA is a viral cell surface receptor of a tetramericglycoprotein nature. It is encoded by 6^{th}gene segment of influenza A genome. Its length is approximately 1413 base pairs in length with slight variations, mature protein size is 454 Daltons.

It consists of four identical polypeptides of approximately 470 amino acids with slight variations in sequence. Four domains of this protein are a membrane-anchoring hydrophobic domain, a thin variable stalk, a globular head domain which is a carrier of enzyme active site and a calcium-binding site [7].

The stalk domain's length varies significantly, and its shortening is associated with adaptation of waterfowl to poultry [8]. Subunits consist of six bladed propeller-like structures, and blades are made up of four antiparallel β-strands [9]. An enzyme active site with conserved charged amino acid residues can be found in the central region of each subunit.

The function of NA is to cleave sialic acid residues from cellular and viral glycoproteins expressed outside the host cell membrane. It is crucial to prevent HA mediated aggregation of newly synthesized viral particles at the surface right after their leakage from damaged host cell, because this would prevent further dissipation. NA fulfills that function by removing newly synthesized HA, which were accidentally bound to sialylatedreceptors of dead cell [10].

Besides the release of budding virion particles through HA release, NA plays a role in promoting cellular infection by promoting glycosylation of the HA and cleaving potential inhibitory Sia-s from mucins. It was shown, that NA recognizes sialic acid residues on host glycoproteins and glycolipids in a different manner in comparison with HA [11].

Different structural features of NA and HA form influenza subtypes.

Neuraminidase subtypes. 10 structurally different NA circulate in birds, which are classified into two main groups [12]. The group 1 includes N1, N4, N5 and N8, and group 2 includes N2, N3, N6, N7 and N9. The classification is based on similar features within the following regions: in the 150-loop (residues 147-152), the 270-loop (residues 267-276), and the 430-loop (residues 429-433), which are regions adjacent to the enzyme's active site.

The only conserved site for all influenza A and B types NA is Asn146 glycosylation region, which is located on the membrane-distal surface close to the active site [13]. Besides that highly conserved region, neuraminidase shows a great diversity in nucleotide sequence, which results in various structural conformations. Mutations incorporated per replication cycle add changes into already present pool of neuraminidase structural diversity.

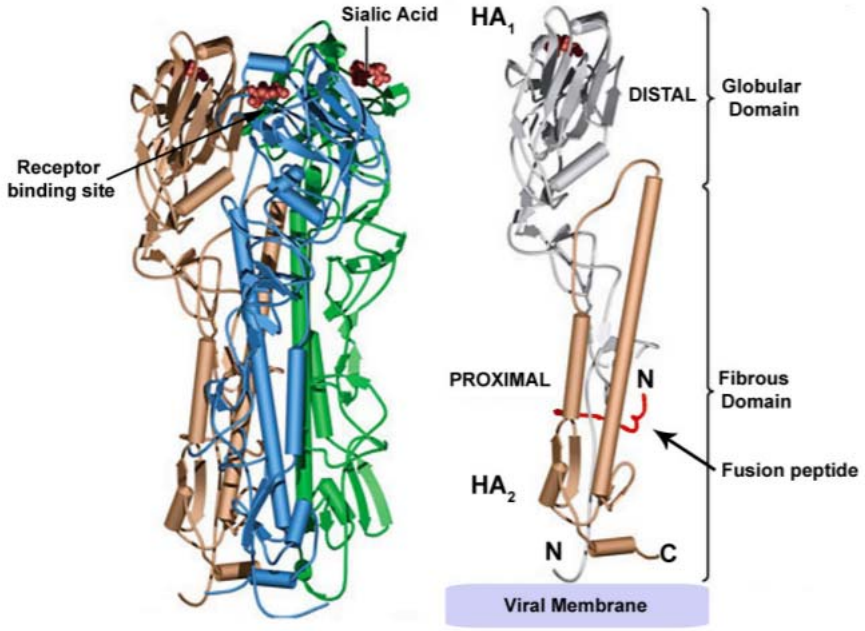
Hemagglutinin. Name of this protein comes from its ability to form aggregates of red blood cells, the carriers of hem – hem agglutinating protein. Widely spread, rapid and moderately sensitive technique of most viruses' identification – is the hemagglutination assay, in which hemagglutinin glycoproteins

clump cells by binding to their surface receptors. There are 18 subtypes of hemagglutinin, and two recent ones H17 and H18 were found in bats [14].

HA is expressed as a trimeric surface receptor on the outside of the viral membrane. It facilitates entry through the receptor binding to the target cell and recognizes sialylated cell receptors for consecutive chemical binding. It is encoded by 4th gene segment of influenza A viral genome with approximately 566 nucleotides in length, although some nucleotide variations are possible.

Sialylated receptor-bound viruses fuse with the cell membrane, and then are engulfed into endosomes once entering cytoplasm. HA becomes acidified by endosomal enzymes, which is followed by conformational changes in its molecular structure and subsequent activation. Different kinds of conformational changes constitute HA subtypes classification system.

The linkage between glycan structures and galactose is crucial in host determination. Avian viruses are characterized by binding to α2-3Sia and are so-called avian-type receptors, while mammalian viruses bind to α2-6Sia and are so-called human-type receptors. However, it should be noted, that cells in human upper epithelium mostly possess α2-6Sia receptors, whereas cells in lower epithelium possess α2-3Sia cell surface receptors. This means that influenza bearing only avian-type receptors is able to cause a moderately mild infection without any serious consequences.



The schematic representation of hemagglutinin structure [15]

However, influenza viruses typically reproduce in cells of human upper respiratory tract through the recognition of sialic acid, or N-acetylneuraminic acid, by HA. N-acetylneuraminicacid is terminated by glycan structures, which are linked to galactose in a β1-4 linkage to glucosamine, and thislinkage in particular is associated with HA recognition and binding to the target cell [10, 16].

The HA is a homotrimer consisting of a globular head with sialic acid binding domain and a fibrous stalk region. Three identical subunits have resulted from proteolytic cleavage of a single precursor, and the process occurs by cleaving single arginine residue extracellularly by serine proteases before entering the host cell. However, some members of H5 and H7 subtypes have acquired several cleaving residues (arginine and lysine), which is partly responsible for H5 and H7 high infectivity and pathogenicity [9].

The coiled-coil structure of the stalk domain stabilizes HA trimers and anchors the protein in the membrane through its transmembrane subdomain [12]. The only conserved amino acid throughout all subtypes of the stalk domain is Lys51.

As it was mentioned before, HA recognizes sialylated cell surface receptors of a target cell, so let's consider these interactions more closely. The interaction occurs through hydrophobic and hydrogen bonding between HA residues from the 130-, 220-loops, 190-helix and sialylated receptors [17].

Sialic acid binding site contains four main structural regions made up from antiparallel β-sheets [12]: a base with highly conserved Tyr98, Trp153 and His183, a 190-α helix (residues 184-190), a 130-loop (residues 126-135) and a 220-loop (residues 215-224) [19].

Amino acids Tyr98, Trp153, His183, Glu190 and Tyr195 directly interact through hydrogen bonding with the side chains of sialic acid, which was shown on H3 subtype in particular.

The 130-loop with crucial residues at 135-137 forms chain interactions with receptor's sialic acid moiety. Mutations within 220-loop constitute differences in host specificity due to slight changes in loop conformation associated with glycosidic linkage type [20]. The 190-helix plays a role in species specificity determination. Double mutations in the HA receptor binding domains of H1N1 at Glu190Asp and Gly225Asp and H2N2/H3N2 at Gln226Leu and Gly228Ser influenza A subtypes are associated with the adaptation of avian viruses into human pandemic viruses.

In addition, four amino acid substitutions of HA in H5N1 at Ser123Pro, Ser133Ala, Thr156Ala, and Gln192Lys are associated with increased binding of the virus to mammalian receptors [20]. Mutation of Asn158 and Thr160 were shown to increase virus affinity to human-type receptors due to the loss of the same glycosylation site on the top of the HA globular head.

In HA2, HA3 and HA9 subtypes Leu226 enables influenza A virus replication in the human airway epithelium.

HA binds to sialic acid through hydrophobic interactions and hydrogen bonding to the conserved amino acids within 130- and 220-loops, although responsible amino acid residues differ from one subtype to another [9]. For example, in HA1, glutamic acid and glycine residues at positions 190 and 225, respectively, are responsible for binding to avian SIA-receptors, whereas HA1 proteins that carry aspartic acid residues at these two positions interact with human SIA receptors. For HA2 and HA3, mutations of Gln226Leu and Gly228Ser correlate with a shift from avian to human receptor specificity [21]. So, slight mutations in amino acid sequenceconstitute the basis of HA subtypes classification.

Hemagglutinin subtypes. Two main groups of 18 HA circulatingin many different hosts are classified according to sequence comparisons and structural characteristics. Group 1: H1, H2, H5, H6, H8, H9, H11, H12, H13 and H16. Group 2: H3, H4, H7, H14, H15 and H10 [22]. The classification also considers conformational changes within HA molecular structure triggered by acidification due to endosomal enzymes functioning.

Ha subtypes could be also relatively classified according to their main host species. For instance, HA1, HA2 and HA3 subtypes circulate mostly in human populations.

A computer analysis by using free access applications has shown close evolutionary relationships between HA subtypes[14]. Very close relationship was shown between HA7, HA15 and HA10 constituting one clade and HA4, HA14 and HA3 constituting another. The common origin was shown for HA8, HA12 and HA9 as well as for HA13, HA16 and HA11[14]. Recently described HA17 and HA18 subtypes show closest evolutionary relations towards another clade including HA1, HA2, HA5 and HA6. This evolutionary relationship formed during last century indicates rapid evolution of influenza viruses due to reassortment between different viral subtypes.

Transition between avian and human influenza types. The transition between avian and human influenza types had occurred several times and had caused several pandemics during human history.

The transition between avian and human influenza types is not so uncommon because of several reasons underlying this process. They include high degree of genetic recombination between different subtypes, error-prone RNA polymerase, which enables a multitude of mutations to occur per replication cycle, rapid generation time of virions and fast replication of virion particles inside of a host nucleus.

The major receptor binding site substitution between avian and human HA10 is Lys137Arg, although some others might also emerge due to incorporation of mutations per replication cycle. Such transitions between avian/swine/human influenza should be studied in details for the trafficking influenza evolution [22].

Conclusion. So far we have discussed some important structural features of HA and NA – envelope proteins responsible for influenza A virus infection occurrence and spread. HA plays a significant role in binding to receptors in host's upper epithelium cells. This is the most common way for a virus to enter a cell. NA's primary function is to release newly synthesized virions from sialylated receptors of host cell. However, NA is also responsible for facilitating HA's glycosylation for viral infection spread. These two

proteins obtain a variety of mutations per replication cycle due to error-prone RNA polymerase. This constitutes a feature of influenza A virus to quickly evolve into new subtypes, which is a great obstacle for modern vaccines. Vaccines are designed mostly against widely spread influenza A pathogens, and if a novel pandemics occurs, the use of vaccines would not be effective.

So, it is very important to understand structural and functional features of influenza A virus proteins to be able to synthesize modern vaccines against it.

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ТҰМАУ А ВИРУСЫНЫҢ МОЛЕКУЛАЛЫҚ ҚҰРЫЛЫМЫНЫҢ БАЗАЛЫҚ ҚАСИЕТТЕРІНІҢ СИПАТТАМАСЫ

Аннотация. Тұмау вирусы – кен таралған вирустардың бірі. Ол жеңіл маусымдық және ауыр пандемияны туғызып, миллионнан астам адамдардың қайтыс болғанына себебші болған. Екі негізгі жасушадан тыс рецепторы – нейраминидаза (NA) мен гемагглютинин (HA) тұмаудың белгілерін дамытуына және аурудың таралуына жауапты.

Қателікке бейімді РНК-полимераза әртүрлі мутацияларды нейраминидаза мен гемагглютининге әр бөлінген сайын енгізе алады. Осы қасиеті тұмауға қарсы көп эффективті дәріні құрастыруды қиындатады. Пайда болған мутациялар вирустыжануарлардан адамдарға жұқтырады. Осы вирустардың типтері өте қауіпті, өйткені мутациялайтын жерлерді алдын ала болжау қиын. Қазіргі таңда вирустарда қандай молекулалық аймағында мутациялар жиі кездесетіндігі анықталды.

Осы мақалада жасушадан тыс рецепторлардың молекулалық құрылымы, қиын аймақтарға рецепторлардың жалғасу механизмдері мен таралған мутациялар аймақтары қарастырылған. Гемагглютинин мен нейраминидаза молекулалық структурасын және қиын аймақтарын зерттеу эффективті вакцина мен дәрілерін дамытуға ықпал ете алады.

Түйін сөздер: тұмау вирусы, нейраминидаза, гемагглютинин, мутация, сиалидаза, вирус.

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БАЗОВЫЕ ХАРАКТЕРИСТИКИ МОЛЕКУЛЯРНОГО СТРОЕНИЯ ВИРУСА ГРИППА А

Аннотация. Вирус гриппа является одним из самых распространенных вирусов в мире. Вирус способен вызывать как умеренные сезонные инфекции, так и пандемии, которые приводят к гибели сотен тысяч людей и животных. Нейраминидаза и гемагглютинин являются основными внешними рецепторами вирусной частицы и участвуют в таких процессах, как проникновение в клетки хозяина и распространение между клетками. РНК – зависимая РНК – полимеразаспособна в процессе репликации допускать ошибки, что приводит к быстрой эволюции вируса и соответственно снижению эффективности разработанных лекарств. Кроме того, высокая мутабельность вируса гриппа приводит к возможности определенного субтипа вируса расширить круг хозяев. Транзитные вирусы являются наиболее опасными и, как правило, способны вызывать пандемии. Однако возможно предсказать какие области генома вируса обладают высокой мутабельностью.

Данная статья описывает молекулярную структуру внешних рецепторов вируса гриппа А, включая рецептор – связывающие сайты и вариабельные участки. Углубленное изучение молекулярной структуры гемагглютинина и нейраминидазы по способствует разработки более эффективных лекарств и вакцин против гриппа.

Ключевые слова: грипп, нейраминидаза, гемагглютинин, мутация, сиалидаза, вирус.

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