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Review Article

Host Cellular Receptors for Some Human Pathogenic Viruses- A Review

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Abstract

The most important and primary factor that is responsible for infectivity in any viral disease is the entry of viral nucleocapsid into the host cell. The viral capsid will attach only on specific sites on the cell membrane depending upon the chemotaxic nature. This article deals with some of the mechanisms of attachment of capsid on the host cell membranes. However, attachment of oncogenic viruses will not be discussed.

Ideally, a virus receptor would fulfill three main characteristics: (1) a physical interaction between the virus and the receptor; (2) occupying the virus-binding site of the receptor (e.g. with an antibody directed against the receptor, should inhibit virus infection); and (3) the cellular sensitivity to virus infection should correlate with receptor expression. Therefore, cells lacking the receptor should not be infected, and transfection with the gene coding for the receptor would confer sensitivity to infection.

Keywords: Variola Virus; Rabies Virus; HIV-1; Hepatitis B Virus; Measles Virus; Japanese Encephalitis Virus; Hepatitis E Virus; Mumps Virus; Polio Virus; Rhino Virus

Introduction

Viruses use specific proteins, glycoproteins, carbohydrate residues of the host cell membrane as attachment sites of their capsid to the membrane. Once the capsid is attached to the cell surface then they will inject their nucleocapsid inside the cell and using the cell's biochemical mechanisms they will multiply. Once there is sufficient number of mature complete virus particles then these will come out of the cell usually by lysis of the cell or sometime by a mechanism called as pinocytosis. The process will continue and the virus will keep the damaging activities going on to increase their number.

HIV-1 receptors

The interest in studying the receptors came up during a very peculiar observation of HIV-1 virus. The CD4 transmembrane protein expressed by a class of T-lymphocytes was a receptor for HIV-1. It was observed that CD4 interacts with high affinity with a glycoprotein [1] of the envelope of the virus-gp120. It was also observed that antibodies against CD4 targeted against binding site of gp120 was blocking the binding of the virus to the lymphocytes [2]. It was concluded that CD4 was not fulfilling all the requirements for binding of the virus. Later on it was observed that CD4 alone was not responsible for the virus attachment. The virus was also capable of binding to cell surfaces of fibroblasts [3], neural [4] and intestinal epithelial cells [5] (which does not produce CD4). It indicated that there must be an alternate receptor other than CD4. This was later found to be an oligodendrocyte marker GalCer [6] which is a glycolipid.

Further studies were conducted on murines (which are thought to be closer to humans phylogenetically) and it was believed that absence of GalCer glycolipid and CD4 in these animals would make them resistant to this virus. However, it was not so. A lot of research was done and it was found that a cofactor fusin (CXCR4) [7] which a G protein coupled transmembrane receptor (belonging to the family chemokine) was responsible for binding of HIV-1 to the murine cells.

Hepatitis B virus receptors

The cells that are the main targets for this virus are the hepatocytes. It was identified that 21 to 47 residues of preS1 (comprising of 10 to 36 amino acid residues in genotype D) are responsible for Hepatitis B virus (HBV) attachment to hepatocytes [8]. However, HBV also attaches to non-hepatocytes like hematopoietic cells like B lymphocytes and peripheral blood lymphocytes [9].

One of the mechanism of HBV getting access to hepatocytes is as shown below.

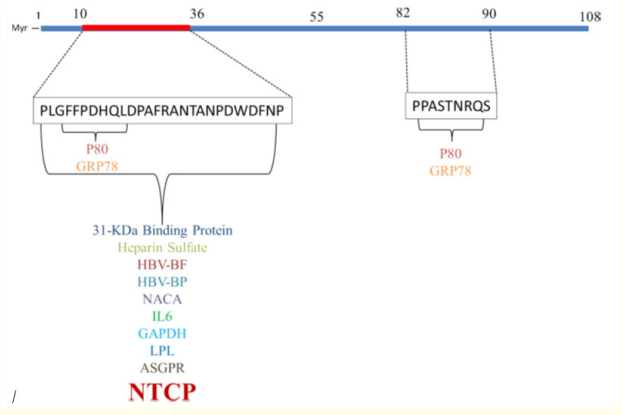

Figure 1: Different interacting proteins that binds to preS1 region of HBV. HBV-BF hepatitis B virus binding factor, HBV-BP hepatitis B virus binding protein, NACA nascent polypeptide-associated complex a polypeptide, IL6 interleukin-6, GAPDH glyceraldehyde 3 phosphate dehydrogenase, ASGPR asialoglycoprotein receptor, NTCP sodium taurocholate co-transporting polypeptide [10].

Later on this PreS1 (having a molecular weight of 44 kDa) was labeled as HBV Binding protein (HBV-BP) and it was having sequence homology to squamous cell carcinoma antigen 1 (SCCA 1) [11] which needs a cofactor Ferritin light chain (FTL). The complex of PreS1-SCCA1-FTL was responsible for entry of the virus into the hepatocytes HepG2.

The next question was how HBV binds to non hepatocyte cells like hematopoietic cell of B lymphocyte lineage. It was shown that Interleukin 6 (IL 6) was the receptor to which HBV binds.

Similarly, it has been observed that HBV and IgA uses the same receptor on cells as the C region of human IgA α1 chain is similar to the binding domain of PreS1 region of HBV.

However, for PreS1 to attach to this site there will be some conformational changes to the receptor on the membrane.

Hepatitis E virus receptors

The hepatitis caused by Hepatitis E Virus (HEV) is the most common cause of acute hepatitis all over the world. The virion exist in two forms 1) naked which is easily passed through stools of infected persons and is transmitted interpersonally [12]. 2) Quasi enveloped which circulates in the blood and is responsible for repeated infection in the same host [13].

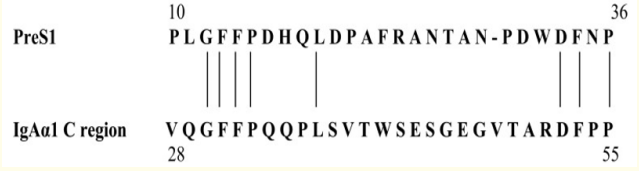

Figure 2: The sequence similarity between preS1 and constant region of IgAα1 [8,9].

It is known that HEV is highly hepatotropic but is capable of infecting other cells like human lung epithelial cells, human colon epithelial cells, neuronal derived cells and human placental cells [14].

The attachment of naked HEV to cells is not clear yet. It is believed that several factors are responsible for attachment to hepatocytes. Some of these are mentioned below.

Heparin Sulfate Proteoglycans (HSGPs): Treatment of the cells with heparinase reduced the binding of the viruses. However, HSGPs) are not essential for attachment to hepatocytes by quasi enveloped HEV particles [15].

Glucose-Regulated Protein 78 (GRP 78) is a molecular chaperone found on the cell surface of mostly hepatocytes. It is also known as binding immunoglobulin protein. It has been implicated in the binding of both naked and quasi enveloped viral particles to cells (especially hepatocytes) [16]. It binds with p239 of both the types of HEV as demonstrated by coimmunoprecipitation [16].

Asialoglycoprotein receptor (ASGPR) which is present on the basolateral membrane of the hepatocytes and binds with glycoproteins which lack sialic acid. There is a direct correlation between ASGPR and HEV particles [17]. This has been demonstrated with HeLa cell lines where HEV binding was seen in presence of ASGPR but when this was removed by coimmunoprecipitation, there was no binding of HEV.

ATP synthase (ATP Synthase 5β subunit) also has been observed to help HEV bind to cell surface since it has been observed as a binding partner of p239 on the viral coat [18].

Integrin α 3 was identified as an entry factor for HEV in PLC/PRF/5 cells [19].

It is hypothesized that after the virus has attached to the cell receptor it undergoes certain structural rearrangements to externalize the hydrophobic peptides of its coat protein which subsequently creates a channel into the endoplasmic membrane for its

genome to enter the cytoplasm of the host cell [20]. This is similar to that of the polio virus.

Regarding the attachment of quasienveloped HEV, it is a different story. It must be remembered that because the virus is enveloped it has no coat protein for attachment to specific receptors of host cells. The envelope has lipids like phosphatidyl serine which might bind to cell receptor like TIM 1 of target cells [21], but this does not do any good for sending in the viral nucleic acid into the host cytoplasm. This sort of nonspecific binding of Quasi enveloped HEV meant that these must be infecting cells other than hepatocytes, more effectively. Rightly so it has been reported to infect neural cells of the central nervous system [22].

It is believed that the quasienveloped HEV is internalized in the cell by a clathrin mediated endocytosis. The virus is then routed through the early RAB 5+ and late RAB 7+ endocytic compartments and ultimately reach the lysosome. Here the lysosomal enzyme slowly degrade the envelope exposing the viral capsid which then penetrates the endosomal membrane to release the genetic material in the cytoplasm of the host cell [23].

Polio virus receptors

The human poliovirus receptor (PVR) has been well studied by many scientist. It is a cell surface protein with a multitude of functions [24]. It was thought to be an integral cell surface protein and its actual identity was elucidated in 1989 [25]. It has been demonstrated that besides being a receptor for polio virus, its other functions are cell adhesion and migration, adaptive immunity and oncogenesis.

Polio caused by polio virus is a neurologic disease when the virus invades the central nervous system. It attacks the motor functions of the spinal cord leading to paralysis (often irreversible) and weakening of the muscles and often leading to death [26].

Human PVR often undergoes splicing generating 4 unique splice isoforms. PVR α, PVR β, PVR γ and PVR δ. Of these PVR β and PVR γ are soluble forms which lack the transmembrane region. Transmembrane forms are found in a variety of tissues like the gastrointestinal tissue, nervous tissue, kidney, lungs tissues etc [27]. Since the extracellular domain of soluble PVR and that of transmembrane isoforms (PVR α and PVR δ) are identical, they compete for the binding of the virus resulting in non-infectivity of the virus [27]. Figure 3 gives the detailed information about the 2 isoforms of the PVR.

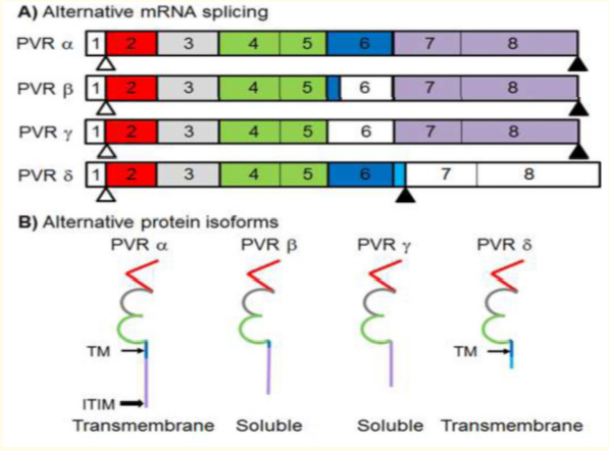

Figure 3: Schematic of exon map for PVR A) RNA spliceforms and B) protein isoforms [27].

Unshaded exons are not expressed in the protein. Exons are color coded to match the portions of the protein that they encode: red = Ig-like domain 1, grey = Ig-like domain 2, green = Ig-like domain 3, dark blue = transmembrane domain (thin arrow/TM), light blue = unique sequence in δ isoform, and gold = C-terminal domain. Start codons appear as white triangles and stop codons appear as shaded triangles. Compared to the canonical isoform PVRα, soluble isoforms PVRβ and γ contain splicing events in exon 6 which result in partial (β) or complete (γ) loss of exon 6. There is an alternative splicing event between transmembrane isoforms PVRα and PVRδ in which an additional eight residues and a stop codon are incorporated at the end of exon 6, resulting in exons 7 and 8 not being translated in PVRδ. The immunoreceptor tyrosine-based inhibitory motif (ITIM) of PVRα is indicated (block arrow).

Rota virus receptors

Rotaviruses, the leading cause of severe dehydrating diarrhea in infants and young children worldwide. These are non-enveloped viruses that possess a genome of 11 segments of double stranded RNA contained in a triple-layered protein capsid. The outermost layer is composed of two viral proteins, VP4 and VP7. VP4 forms spikes that extend from the surface of the virus and has been associated with a variety of functions, including the initial attachment of the virus to the cell membrane and the penetration of the cell by the virion.

Rotaviruses have very specific affinity for cells. They would attach to the epithelial cells on the tips of intestinal villi [28]. *In vitro* they would exhibit specific affinity to epithelial cells of renal or intestinal origin. In certain animal strains the virus was showing af-

finity for sialic acid present on the surface of epithelial cells. There is very scanty information available as to the exact nature of the cell receptors.

However, it is hypothesized that rotavirus receptor is a complex of several cell (surface) components which includes gangliosides, N-linked glycoproteins with other proteins in lipid rafts which might need other lipid microdomain to function efficiently in binding and internalization of rotavirus particles [28].

Rabies virus receptors

The rabies virus is very well adapted to the mammalian nervous system, where it mostly infects neurons. It is believed that the virus is transmitted to humans through infected animal bites and sometime through aerosol. The entry is through a sensory nerve or through a spindle of nerves at the neuromuscular junction, where motor axons bifurcate in invaginations of the muscle surface [29]. After crossing the neuromuscular junctions, the virus is found in both neutral and acidic vesicles which mean that there is fusion of the virus envelopes thus releasing nucleocapsids in the axoplasm [30].

The viral envelope is made up of host lipids and two proteins G and M. The G protein is a membrane glycol protein with three N-glycosylation sites. It becomes a trimer in the endoplasmic reticulum of the host cell. This G protein helps the virus to attach to the host cell surface. After this it is transmitted to the CNS by the retrograde pathway [29] which is the job of the lentivirus.

There are several different molecules which facilitates the attachment of the Rabies virus G (or the lentivirus) on nerve cell surface. These are discussed below.

Nicotinic acetylcholine receptor (nAChR), which is located in post synaptic muscle membrane and by attaching to this molecule, the viral inoculums gets amplified before it enters the nervous system. Alternatively, nAChR might help to concentrate the viral particles at the neuromuscular junctions thus facilitating better uptake of the particles by the nerve terminal [30].

The Neuronal cell adhesion molecule (NCAM)is a glycol protein from the immunoglobulin superfamily Three major splicing isoforms are expressed on the surface of the cells: a glycosyl phosphatidylinositol linked NCAM 120, and two transmembrane forms NCAM 140 and NCAM 180 which have cytoplasmic tails of different lengths. They all contain the same ectodomain i.e. five immunoglobulin like and two fibronectin like domains. It has been observed that laboratory cell lines susceptible to rabies virus infection express NCAM on their surface which is unlike in case of resistant cells which do not have NCAM on their surface. If antibodies against are used to neutralize NCAM and also if the virus is treated (incubated) with soluble NCAM then the infectivity reduces drastically indicating that NCAM is a part of cell surface receptor [29].

It was previously thought that p75 neurotrophin receptor found on the cell surface could be a cell receptor for Rabies lentivirus G as it was binding to the viral particles when incubated *invitro* with fibroblast cell lines. However, there is no proof of the same *in vivo* tests [48].

It was also observed that fibroblasts desialylated with neuraminidase could not bind to rabies virus but when the cell lines were fed with gangliosides GT1b and GQ1b could again be infected with rabies virus [31].

Measles virus receptors

Measles virus (MeV) is a paramyxovirus that contains a 15 kilobase non-segmented RNA genome encoding nucleocapsid protein (NP), phosphoprotein (P), virulence factors (C and V), matrix protein (M), membrane fusion protein (F), hemagglutinin (H), and an RNA dependent RNA polymerase (L) [32]. The virus possesses a membrane envelope which contains the two viral glycoproteins, H and F. H protein mediates attachment to the host cell receptor, while F directs fusion of the viral envelope with host plasma membrane and syncytia formation, leading to cytopathic effects and cell death.

The first step is binding of the H protein to cellular receptor. This is followed by fusion of the virus with host cell membrane brought about by the F protein [33]. The cellular receptor was discovered to be CD46 to which MeV was attaching first. It was a complement binding protein also called as membrane complex protein [34]. CD 46 protein is comprised of four short conserved regions (SCR1-SCR4), the Ser/Thr/Pro (STP) domain, transmembrane region, and two alternatively spliced cytoplasmic tails.

It was observed that a single tyrosine molecule at residue 481 of MeV-H determined high affinity for CD 46 but binding to putative lymphocyte was favored when asparagines was at this position [36].

Other receptor include signaling lymphocyte activation molecule family 1 (SLAM F1) as the lymphocyte receptor for MEV [37].

MeV is also known to cause certain carcinoma of epithelial cells. These are the small airway epithelial cells. The receptor for MeV

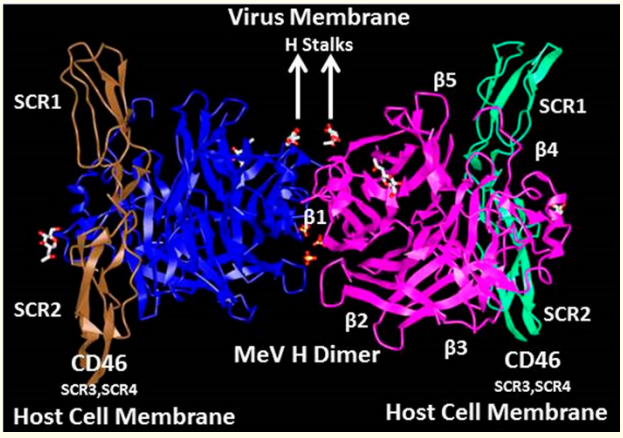

Figure 4: Structure of SCR1 and SCR2 domains of CD46 bound to H protein dimer head region [35].

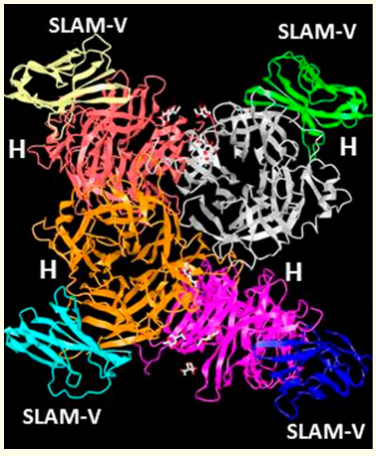

Figure 5: Structure of SCR1 and SCR2 domains of CD46 bound to H protein dimer head region [35].

to attach to these epithelial cells are Nectin-4 or PVRL4. These are usually adenocarcinoma type of oncogenesis.

Mumps virus receptor

Mumps virus (MuV), an important aerosol-transmitted human pathogen, affects the parotid and other salivary glands, pancreas, testis, ovary, mammary glands, and kidney [39]. It also infects the central nervous system, causing meningitis and, less frequently, encephalitis and unilateral nerve deafness. It is classified in the same group as Measles virus. It has been proven beyond doubt that MuV hemagglutinin-neuraminidase (MuV-HN) forms a complex with a 2,3-sialylated trisaccharide in addition to the interaction between the MuV-HN active site residues and sialic acid, other residues, including an aromatic residue, stabilize the third sugar of the trisaccharide [40]. It was also observed that MuV-HN bound more efficiently to unbranched a 2.3-sialylated sugar chains compared to the branched ones. The aromatic residue played a vital role as it was conserved among the HN proteins of sialic acid. Alanine substitution was playing a compromising role to support cell-cell fusion. The abundance of structurally different sialylated glycans in tissues and organs helps to explain why MuV has distinct affinity for glandular tissue and the central nervous system [41].

Receptors for rhinoviruses

Human rhinoviruses (RVs) are picornaviruses that can cause a variety of illnesses including the common cold, lower respiratory tract illnesses such as bronchitis and pneumonia, and exacerbations of asthma. RVs are classified into three species, RV-A, B [42] and C [43]. These viruses use certain glycol proteins like intercellular adhesion molecules 1 (ICAM 1) which is used by most of RV-a and all RV-B. Low density lipoprotein receptors used by some RV-A. Cadherin (CDHR 3) used mostly by RV-C. CDHR3 belongs to a superfamily of transmembrane proteins and their exact biological role is unknown. It is demonstrated that a single nucleotide polymorphism (rs6967330) in CDHR 3 will result in RV-c infection in infants which will result in improper lung development and finally leading to development of asthma as the child grows up.

RV-A and RV-B utilize several cellular receptors in order gain access in the cytoplasm. Once attached it then enters the cell by endocytosis. This have been extensively studied in model cell lines like HeLa cell lines [44]. The endocytosis is clathrin and dynamin dependent [45]. However, the mechanism for RV-C is not yet known. The other alternative receptor that is often employed in case of absence of ICAM1, by some RV-A is the heparin sulfate. In this case it is essential that dynamin be available but not clathrin, caveolin or flotillin [46].

The major group RV cellular receptor ICAM-1 was identified in 1989 by three independent research groups [47] and five years later followed by the discovery of LDLR family members as the receptors for minor group rhinoviruses, which includes only few known RV-A [48]. Actually ICAM-1 is not responsible for internalization of the virus but LDLR does help in internalization in the endosome [49].

RV entry in primary airway epithelial cells which is the most natural host is not fully understood. Some claim that it is clathrin mediated endocytosis [50]. Some other researchers claim that RV infects nasal mucosa by ceramide enriched ganglioside type 1,

membrane platform and is independent of clathrin and dynamin [51].

Human cadherin-related family member 3 (CDHR3) protein mediates virus binding and replication in normally unsusceptible cultured cells [52]. It is very important receptor for RV-C infecting infants leading poor lung development.

It is believed that RV enters cytoplasm of host cell by destabilizing the endosomal membrane and by rupture. Some have hypothecated that the ion channels too play an important role of entrance into the cytoplasm [53].

Japanese encephalitis virus receptor

Japanese encephalitis virus (JEV) is a mosquito borne flavivirus causing acute viral encephalitis in humans. The other well-known flavivirus is the dengue virus again spread by mosquitoes. The only other encephalitis virus (flavivirus) that is a human pathogen is tick borne [54].

It was known that like many of the flavivirus like dengue virus, West Nile virus and yellow fever virus uses the clathrin mediated method of internalization in specific host cells, and that JEV too must be using this method of internalization involving endocytosis [55]. Later on it was seen that the actual entry of JEV was not clathrin mediated but dynamin-2 dependent [56]. Dynamin-2 is a GTPase which is responsible for release of newly formed endocytic vesicles from plasma membrane. The further process is completed by a transport protein - transferrin. Though clathrin is not required for JEV internalization but a membrane lipid - cholesterol is highly essential [56]. Next, it was found that small GTPases like Rho isoform RhoA had a significant role in endocytic internalization and infection of JEV in neuronal cells. After internalization of JEV it further activates Rho-A in neuronal cells [56]. After the endocytosis, the mileu in the endosome must be acidic for the virus to release the RNA [57]. In order to do this it passes through Rab-5 (early endosome). However, It does not require the late endosome-Rab-7. Finally in order to enter the endosome and get endocytosed for internalization it goes through very specific sites on the plasma membrane of neurocells and the determinant for this is the Glucose regulated Protein 78 (GRP-78) [58].

Influenza virus receptor

Just after the first world war in 1918, the world was under a grip of a deadly pandemic was taking heavy toll on human lives. It was nothing but the Spanish Flu caused by a virus called influenza virus (H1N1) [59].

Figure 6A: A photograph from the archives showing patients in a hospital ward suffering from Spanish Flu caused by H1N1 virus [59].

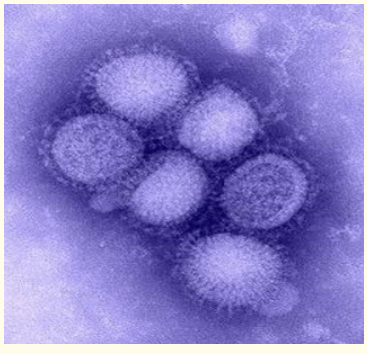

Figure 6B: Particles of influenza virus H1N1 [59].

Since then lot of research activities have taken place and lots of literature reviews can be found on the internet. The first finding was that the influenza virus has two important antigens on their protein coat and these are hemagglutinin and neuraminidase. Hemagglutinin is a glycoprotein which binds to the sialic acid residue on the cell membrane and is responsible for internalization of the virus inside the cells preferably of lung parenchyma and other tissues of upper respiratory tract and the job of neuraminidase (which is actually a sialidase) is to cleave this sialic acid with the virus to help it in spreading [60]. There are different antigenic variants of hemagglutinin and neuraminidase and this is reflected in different types of influenza viruses. The latest reported one is H7N9 which is transmitted in a zoonotic manner to humans from its parent source the aves and hence it is also called as the avian flu virus [60]. However, the basic mechanism of internalization of the pathogen remains the same.

Beside this the neuraminidase also has a separate binding site called as the hemadsorption site on the cell membranes which is

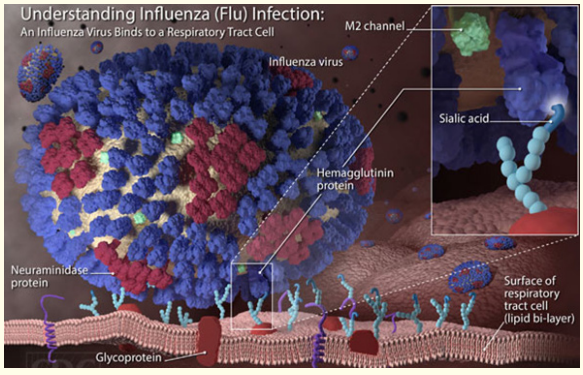

Figure 7: Binding of Hemagglutinin to receptor cells [60].

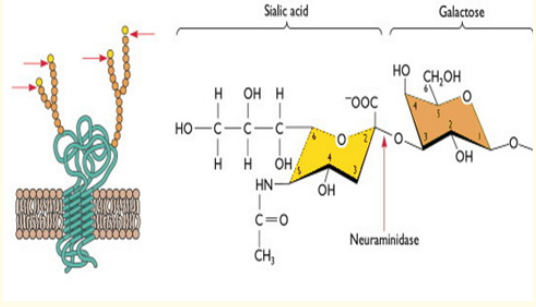

Figure 8: Cleaving the sialic acid from the galactose residue. The red arrows indicate that the sialic acid residues (indicated as hollow circles) present at the terminal end of the glycan residues (the binding site for hemagglutinin).

other than its sialidase site [60]. This has been observed especially in case of H7N9 avian flu virus as a causative agent of influenza in humans [60].

Small pox virus receptors

Small pox virus or the Variola Virus (VaV) is the causative agent of the devastating disease of humans - Small Pox. It was finally eradicated in 1980 by mass vaccination using another pox viral antigen that is vaccinia virus (causing cow pox) [61]. This also marked the end of research activities on VaV. The mechanism of pathogenesis is still not well studied as of date.

It has been observed that VaV and some herpes viruses which have large DNA molecule as nucleocapsid is capable of producing a secreted version of host receptor binding proteins, which is capable of sequestering the cytokines and neutralizing these to evade the host immune system [62]. One such protein was the VaV Tumor Necrosis Receptors (vTNFRs) which was responsible for blocking the activity of the proinflammatory activity of the cytokines. These are examples of viral receptors with sequence similar to the extracellular cytokine-binding domain of their cellular counterparts [63]. This protein is a 35kDa chemokine which is capable of binding to CC chemokine and is common to variola and vaccinia virus [64].

It was later discovered that VaV which causes human and monkey small pox virus had a gene which could code for Cytokine response modifier B (Crm B) protein which is a vTNFR [65]. The reason for this is not known though it has been reported that there are 4 Crm proteins viz. Crm B, Crm C, CrmD and Crm E which are produced by a variety of pox viruses. Usually the ligand binding region of cellular TNFRs are cysteine rich but the CrmB and CrmD have C-terminal domain (CTD) which is not related to host protein [63]. Therefore, the vTNFR of VaV (which is Crm B) is just not a ordinary TNFR but plays a role to inhibit the host chemokine using its CTD.

Conclusion

It is by knowing the host cellular receptors; primary designing of drugs capable of preventing the attachment of the virus particle to the receptor will be feasible. Later on more detailed studies like the most probable toxicological studies and other pharmacokinetic and pharmacodynamic studies will be essential for effective delivery of the drug molecule to the site of action.

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