**Abstract**

Viruses have utilized elegant strategies in order to connect to multiple receptors on host cell surface during internalization and infection steps. Among them, viral attachment proteins play vital role in the case of inter-molecular interaction with host cell surface receptors, which mediates activated entry of virus into the host cells. Consequently, a wide range of common viral receptors including sialylated glycans, phosphatidylserine receptors, immunoglobulin superfamily members and integrins as main cell adhesion molecules have been emerged for virus crossing events. The redundancy in virus internalization mechanisms because of targeting particular receptors on host cell surface provides favorable cross-species and quickly transmission to new hosts. Due to the importance of complexity nature of virus internalization during viral pathogenesis and redundancy in the synthesize of diverse member of attachment proteins, the virus-receptor conception would be an attractive issue for newly antiviral therapeutics. Therefore, in this review we will highlight the functionality of different classes of host cell receptors during viral entry/pathogenicity and ongoing clinical challenges.

**1. Introduction**

Specific cell surface receptors recognition and inter molecular interactions as very critical multistep processes facilitate epithelial barrier across and successful internalization of the virus into the host cells. Viruses as obligate pathogens can access host cells machinery during infectious life cycle and quickly spread between human [1-4]. Tropism, pathogenesis and developed infectious life cycle of virus are governed by intermolecular forces (mainly electrostatic and non-specific) with a wide range of cell surface receptors molecules [5, 6]. Cell membrane receptors not only pose fundamental attachment sites for a large number of viruses, but also exploit extended structural changes that lead to potential intracellular trafficking of virus and activated signaling events. Eventually, such changes in cell surface structure coordinate crossing cellular barrier and initiating infectious life cycle for transmit to new host tissue. The simple situation of virions internalization into host cells may be obtained through effectively virus targeting by receptors moieties to assist endocytosis-mediated mechanism [5, 7]. Alternatively, receptor moieties may directly cause significant cellular attachment/internalization events via activating the specific signaling pathway or inducing conformational alterations in virions structure [3, 8]­. Therefore, studying detailed entry mechanism of viruses which are mediated by overexpressed cell surface receptor moieties and attachment proteins, has provided new insights into the development of newly diagnostic methodologies and antiviral therapeutics [5, 7]. The identification of viral receptors molecules are significantly conducted by applying applicable *in vitro* techniques such as solid-phase assays, perturbation of targeted gene, orbital mass analysers with high-resolution, affinity purification monoclonal and anti-idiotypic antibodies. The entry of several virions like influenza A virus is also facilitated using single-receptor fusion, while some other virions entry into host cells and initiate infectious life cycles through multi-receptors interaction on the same or different cells surface (such as both signaling pathway of activated lymphocyte molecule and nectin-4 receptor for internalization of measles virus) [1, 5, 7]. There are various types of attachment glycoproteins and glycolipids, such as spike-like proteins (in coronavirus) and heparan sulphate that are specialized in the recognition of host cell surface receptor moieties and interspecies transmission of virions [9, 10]. Spike-like proteins as very important membrane glycoproteins as key determinants of host cell surface structures, has high specificity attributable to cell surface receptor moieties in comparison to viral capsid protein that encapsulated into spherical capsid [4, 11]. Functionality of spike-like proteins in order to interact with receptors molecules originate from domain near the N-terminal (S1) owning to a helical structure followed by transmembrane carboxyl domain near C-terminal (S2) that mediates virions fusion to cell membrane [9, 10]. Novel and traditional comparative studies have revealed the importance of various spike-like proteins in organ tropism, *in vivo* pathogenesis and changes in virions virulence. Targeted RNA recombination technology showed that differing in the gene sequence of spike and appearance the large number of spike-like protein variants have significant effect on *in vivo* virulence [9, 10]. As before explained, spike-like proteins contain two functional domains (exempliﬁed S1 and S2 domain) that alterations within S1 domain (as viral-receptor binding domain) are unequivocally originated from extreme variability in natural genetic of S1 fragments. While, S2 changes are broadly appeared in mutants owning to newly infectious properties [12-14]. Therefore, this information supporting a role of both viral-receptor molecules recognition and cell membrane fusion events in the case of virions pathogenesis outcome. In this regard, it is likely that interaction between virus and receptor can exhibit a range of low to high affinity binding outcome. In the first step of virions infectious life cycle, viruses usually engage a range of receptor in low affinity through avidated interactions like electrostatic forces followed by subsequent intermolecular interactions with more specialized receptor in high affinity events. It seems that, initiate low affinity interactions between virions and host cells could be mediated by cross interactions with carbohydrates moieties inluding sialylated glycans or sialic acids (SAs) [7]. Because of the importance of virus’s receptors, studying distributions of various types of receptor components and their engagement in virus’s fusion and entry events can provide useful and wealthy information about novel and applicable antiviral therapeutics. Therefore, in this review we will summarize the current information of specific receptor molecules which are broadly exploited by several viruses during *in vivo* pathogenesis outcome [7].