12 (2021) 200227

Contents lists available at ScienceDirect

Tumour Virus Research

journal homepage: www.journals.elsevier.com/tumour-virus-research

Potential entry receptors for human γ-herpesvirus into epithelial cells: A plausible therapeutic target for viral infections

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ARTICLE INFO

Keywords:
Eph
Epithelial cell
Herpesvirus
gHgL
KSHV
EBV
Pathologies

ABSTRACT

Herpesviruses are ubiquitous viruses, specifically the Epstein Barr virus (EBV). EBV and Kaposi's sarcoma-associated herpesvirus (KSHV) establish their latency for a long period in B-cells and their reactivation instigates dreadful diseases from cancer to neurological modalities. The envelope glycoprotein of these viruses makes an attachment with several host receptors. For instance; glycoprotein 350/220, gp42, gHgL and gB of EBV establish an attachment with CD21, HLA-DR, Ephs, and other receptor molecules to hijack the B- and epithelial cell machinery. Ephs are reported recently as potent receptors for EBV entry into epithelial cells. Eph receptors play a role in the maintenance and control of various cellular processes including morphology, adhesion, proliferation, survival and differentiation. Alterations in the structure and expression of Eph and ephrin (Eph ligands) molecules is entangled with various pathologies including tumours and neurological complications. Along with Eph, integrins, NRP, NMHC are also key players in viral infections as they are possibly involved in viral transmission, replication and persistence. Contrarily, KSHV gH is known to interact with EphA2 and -A4 molecules, whereas in the case of EBV only EphA2 receptors are being reported to date. The ELEFN region of KSHV gH was involved in the interaction with EphA2, however, the interacting region of EBV gH is elusive. Further, the gHgL of KSHV and EBV form a complex with the EphA2 ligand-binding domain (LBD). Primarily by using gL both KSHV and EBV gHgL bind to the peripheral regions of LBD. In addition to γ-herpesviruses, several other viruses like Nipah virus, Cedar virus, Hepatitis C virus and Rhesus macaque rhadinovirus (RRV) also access the host cells via Eph receptors. Therefore, we summarise the possible roles of Eph and ephrins in virus-mediated infection and these molecules could serve as potential therapeutic targets.

1. Introduction

There are more than 130 viruses has been classified under the *Herpesviridae* family which are known to infect mammals, birds, fish, reptiles, amphibians, or even molluscs [1]. The *herpesviridae* subfamilies like alpha (α), beta (β), and gamma (γ) are known to infect humans and they are categorised based on their replication strategies, host range and genetic organization [2]. The α-herpesviruses include herpes simplex virus (HSV) 1, -2 and varicella-zoster virus (VZV); β-herpesviruses contains cytomegalovirus (CMV), human herpesvirus (HHV)-6 and -7 while γ-herpesviruses includes Epstein Barr Virus (EBV)/HHV4 and Kaposi sarcoma-associated herpesvirus (KSHV)/HHV8 [3]. Herpesviruses are so ubiquitous that one or more herpesviruses infect almost all humans during their lifespan. Virus infection to the host involves a complex multi-step process, the first step being the virus attachment to different host cells using distinct sets of viral glycoproteins. Upon attachment, the processes of viral fusion and entry are initiated. For instance, EBV infection of epithelial cells mainly relies upon the interaction of gHgL with host surface integrin molecules (αvβ5, αvβ6, and αvβ8) [4,5], neuropilin (NRP1), non-muscle myosin heavy chain-IIA (NMHC-IIA) and the recently reported erythropoietin-producing human hepatocellular (Eph) receptors [5]. KSHV is also known to utilise Eph and ephrins as attachment or entry receptors [5]. The binding of the viral proteins to the host receptors can trigger conformational changes leading to membrane fusion [6]. Eph is involved in multiple life processes and several diseases, and at the same time it is closely related to viral infections. Under normal physiological conditions, these receptors regulate various

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https://doi.org/10.1016/j.tvr.2021.200227
Received 29 July 2021; Received in revised form 28 October 2021; Accepted 15 November 2021
Available online 18 November 2021

Abbreviations

Erythropoietin-producing human hepatocellular receptors Eph
Kaposi sarcoma-associated herpesvirus KSHV
Epstein- Barr virus EBV
Sarcoma Src
Ras homolog family member A RHOA
Ras-related C3 botulinum toxin substrate 1 (RAC1)
Cell division control protein 42 CDC42
Signal transducer and activator of transcription 3 STAT3
Phosphatidylinositol 3-kinase/Protein kinase B PIK3/PKB
ADP-ribosylation factor 1 Arf1
Growth factor receptor-bound protein Grb
Neuropilin NRP1
Non-muscle myosin heavy chain IIA NMHC-IIA
Hendra virus HeV
Nipah virus NiV
Mòjiāng virus MojV
Cedar virus CeV
African henipavirus HNV
Hepatitis C Virus HCV
Rhesus macaque rhabdovirus RRV
Human gammaherpesvirus 8 HHV8
Herpes simplex virus HSV
Varicella-zoster virus VZV
Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin DC-SIGN
Heparan sulfate HS
Focal adhesion kinase FAK
c-Casitas B-lineage Lymphoma c-Cbl
Adaptor protein 2 AP2
Epidermal growth factor receptor substrate Eps15
Tyrosine kinase domain TKD
Sterile alpha motif SAM
Clathrin-dependent endocytosis CME
Mouse pulmonary microvascular endothelial cells MPMECs
Glutamate/cystine exchange transporter X-CT
Ras homologous-guanosine triphosphatase Rho-GTPase
Heparin-binding domains HBD
Extracellular matrix ECM
HMVEC-d (human microvascular dermal endothelial cells)
HFF cells (human foreskin fibroblasts)
Chinese hamster ovary (CHO)
Sindbis virus (SINV), Human immunodeficiency virus HIV
Kaposi's sarcoma KS
Primary effusion lymphoma PEL
Multicentric Castleman's disease MCD
Virus influenced inflammatory cytokine syndrome KICS
B-cell lymphoma cells BJAB
Receptor tyrosine kinase RTK
Erythroblastic oncogene B2 ErbB2
Latency-associated nuclear antigen LANA
Fas-associated death domain-like interleukin-1β-converting enzyme-inhibitory protein vFLIP
G protein-coupled receptor vGPCR
Fibroblast growth factor receptor 1 FGFR1
Burkitt lymphoma BL
Complement receptor type-2 CR2
Human leukocyte antigen-DR isotype HLA-DR
Epidermal growth factor EGF
Nasopharyngeal epithelial cells NPECs
Vascular endothelial growth factor VEGF
Diffuse large B-cell lymphoma DLBCL

embryonic developmental events, such as migration of neural crest cells, axon guidance, boundary formation, vasculogenesis and segmentation of the hindbrain [7,8]. Particularly in the brain, vital processes such as neuron-glia communication, early brain development and myelination are regulated by Eph signalling [9–11]. Eph-ephrin signalling is also evident in the maintenance of cell-cell junctions.

Briefly, Ephs are the largest subfamily of tyrosine kinase receptors, which are divided into 2 subclasses, A and B; based on their ligand-binding preferences [12,13]. There is a total of nine EphA (EphA1-A8 and EphA10) and five EphB (EphB1-B4 and EphB6) receptors known in humans (Table 1) [7,14,15]. Additionally, there are six A-subclass ephrins ligands (ephrin-A1 to ephrin-A6) and three B-subclass ephrins (ephrin-B1 to ephrin-B3) which interact with EphA and B receptors, respectively (except for EphA4, which can interact with both A- and B-subclass ephrins) (Fig. 2) [16]. The interaction of Eph receptors with ephrins trigger unique bidirectional signalling to mediate the process of communication between the cells [17,18]. Eph and ephrin molecules are often overexpressed in numerous types of malignancy like breast cancer, skin cancer, colorectal cancer, melanoma and neurological complications such as encephalitis, meningitis and neurodegenerative diseases [19–21]. In human herpesviruses, Eph receptor is reported as a potent entry receptor for several pathogens including γ-herpesviruses. A mitigated expression of the Eph receptor (EphA2 and B4) was observed in HCMV infection to fibroblast cells. The reduced expression of Eph receptors in infected cells suggested that HCMV might limit ephrin mediated cell-to-cell communication and eventually immune evasion [22,23]. Besides, non-human herpesvirus like Rhesus macaque rhadinovirus (RRV) is known to use 10 different Ephs for establishing the infection (Table 1) [6]. The detailed process of herpesvirus entry through Eph and ephrin molecules is explained in the further sections of the review. Additionally, viruses belonging to the *Paramyxoviridae* family, Henipavirus genus [Hendra (HeV) virus, Nipah (NiV) viruses, more recently discovered Mòjiāng virus (MojV), Cedar virus (CeV) and African henipavirus (African HNV) [24,25] take advantage of Eph and ephrin molecules as attachment and entry receptors. In particular, HeV and NiV use ephrin-B2 and -B3 whereas CeV and African HNV utilise

Table 1
Illustration of Eph receptors used by different viruses to enter into the host cell (Eph A10 and -B6 are pseudokinases).

Ephs	Virus (Viral component)	Interacting viral protein (domain)	References
A2	EBV (gHgL), KSHV (gHgL), HCV (NS5A/S5B), CedV	N-terminal domain of gH NS5A/S5B (MSP domain)	[20,37–40]
A4	EBV (gHgL) KSHV (gHgL), RRV (gHgL)	N-terminal domain of gH	[20,32,39,41]
A5	RRV (gHgL), HCV (NS5A/NS5B), CedV	N-terminal domain of gH	[24,32,37,39]
A7	RRV (gHgL)	N-terminal domain of gH	[20,24,32,39]
B1	CedV (G protein)	Receptor binding domain (Residue K209–C622)	[13,20,42]
B2	RRV (gHgL), NiV (G protein), CedV	G–H Loop of G-protein	[20,24,32, 43–45]
B3	NiV (G protein), RRV (gHgL)	G–H Loop of G protein	[20,32,43]

only ephrin-B2 [26]. HeV and NiV infection cause respiratory and neuronal diseases in humans and other animals [27,28]. Whereas, CeV G-protein can bind with different host receptors such ephrin-A2, -A5 and -B1 which is possibly due to the structural differences in the receptor-binding pocket (Table 1) [13,29,30]. Likewise, an siRNA-based study revealed the function of EphA2 as a cofactor in Hepatitis C Virus (HCV) entry [31]. Further, the attachment of the virus to the host cell may aid in virus endocytosis by manipulating the signalling pathways [32].

Here we have focused on the crucial yet unaddressed role of epithelial entry receptors in herpesvirus infection particularly as an attachment and fusion factor that can further result in directing of several cytosolic proteins. As EBV is a ubiquitous virus it remains silent in the cells (lymphocytes) and its reactivation triggers several malignancies and neurological ailments. Likewise, KSHV is also a carcinogenic virus having high cellular tropism. The increased revelations of herpesvirus-associated pathologies need desperate attention. Thus, it is crucial to understand their entry mechanism, so that the viral entry into the host cells can be blocked. Otherwise, the blockage of viruses after entry will also modulate host cell downstream mechanisms and

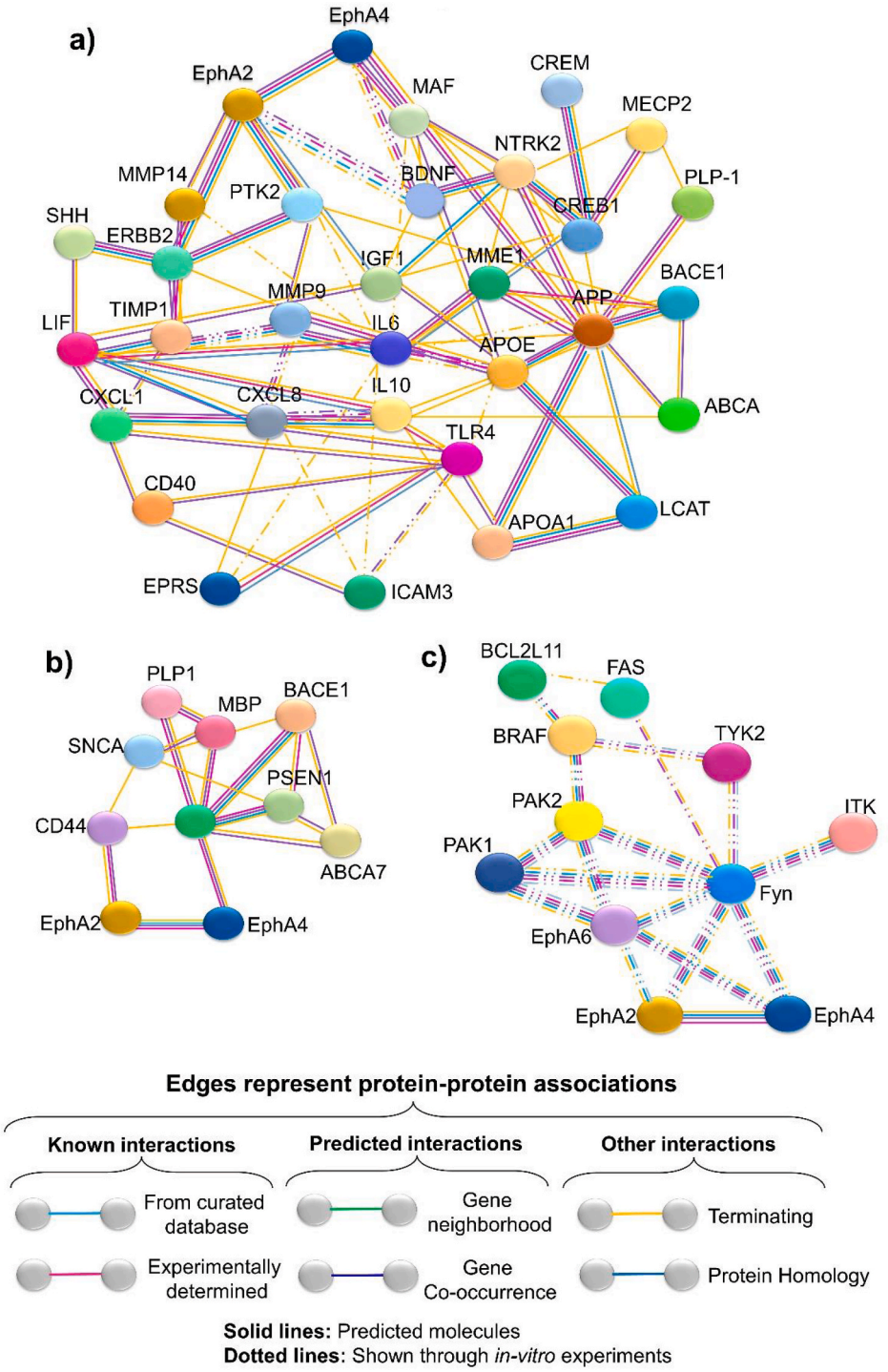

Fig. 1. Ephs (EphA2 and -A4) interaction with different epithelial cell regulatory proteins upon EBV infection in different cell lines (figure shown through protein-protein interaction by using STRING and amendments were included manually); **a)** U-87 MG cells **b)** HMC-3 cells **c)** AGS cells.

increase the likeliness of pathologies. Few reports from our group hint towards an altered profile of several biomolecules in epithelial cells like microglial (HMC-3), astroglia (U-87 MG) and gastric carcinoma (AGS) cell lines upon EBV infection [33–35]. In the aforementioned study, the authors have also correlated the regulatory genes that may be involved in the altered biomolecular profile. Interestingly, several molecules found in the above investigation have a relation with Eph receptors. Fig. 1 is the short depiction of Eph receptors interact with the altered molecule profile [36]. We strongly believe that the amended profile of these biomolecules has a connection with different entry receptors of EBV (Fig. 1). Furthermore, to the best of our current knowledge there is no available literature review that could explain these key points cumulatively. Therefore, here we attempt to narrate the study of different receptors used by human γ-herpesviruses. Moreover, in herpesviruses the recently reported receptor (Ephs receptor) could be the plausible drug target against virus infections. Nonetheless, we also looked at the possible therapeutics that could target Eph receptor signalling pathways.

1.1. Involvement of γ-herpesviruses proteins in epithelial cells attachment and entry

KSHV or HHV8 virions are surrounded by a lipid bilayer envelope ornamented with virally-encoded glycoproteins such as gB, gHgL, K8.1 A/B, gM and gN which help in establishing the virus and host cell interaction [46]. The gB, gHgL, gM, and gN of KSHV share homologies with other herpesviruses like EBV, HSV and VZV [46]. Among the KSHV glycoproteins, gHgL and gB are the most studied. KSHV gHgL and gB make an initial attachment with epithelial cells by several receptors mentioned subsequently. The gH null mutant of KSHV showed to have a role in infection and determining the range of KSHV *in vitro*. KSHV infection into epithelial, endothelial, and fibroblasts cells require gH, as evidenced by the gH-null mutants that were unable to infect the target cells (Fig. 2) [47]. KSHV gH is indispensable for infecting human and nonhuman epithelial, endothelial and fibroblasts cells, whereas it is found to be dispensable for viral replication, maturation, and in virus egress [48]. The latently infected B-cells are the major reservoir of KSHV [49,50]. KSHV with gH null mutant showed low efficiency of infection to the MC116 B cell line, though its role in human B cell infection is still elusive [48]. Likewise, other human γ-herpesvirus, i.e., EBV is also known to infect lymphocytes and epithelial cells. The mechanism of EBV entry into the B cells is well documented; however, the knowledge of how exactly EBV takes entry into the epithelial cells is still a topic of debate [51]. In the case of B-cells, EBV envelope gp350 is known to establish initial interaction with complement receptor type-2 (CR2). The interaction is followed by priming of a trimeric protein complex (gH, gL and gp42) to human leukocyte antigen-DR isotype (HLA-DR) and virus fusion using gB (Fig. 2) [52,53]. EBV gp42 is indispensable for B cell infection [54,55]. Unlike B cells, epithelial cells lack the constitutive expression of CR2 and HLA class II molecules. So, the EBV attachment with epithelial cells can be triggered by gp350, but on CR2-negative cells the attachment is also mediated by a dimeric protein complex, the gHgL. Apart from attachment, EBV fusion with an epithelial cell requires gB along with gHgL complex [56]. The anti-gHgL monoclonal antibody

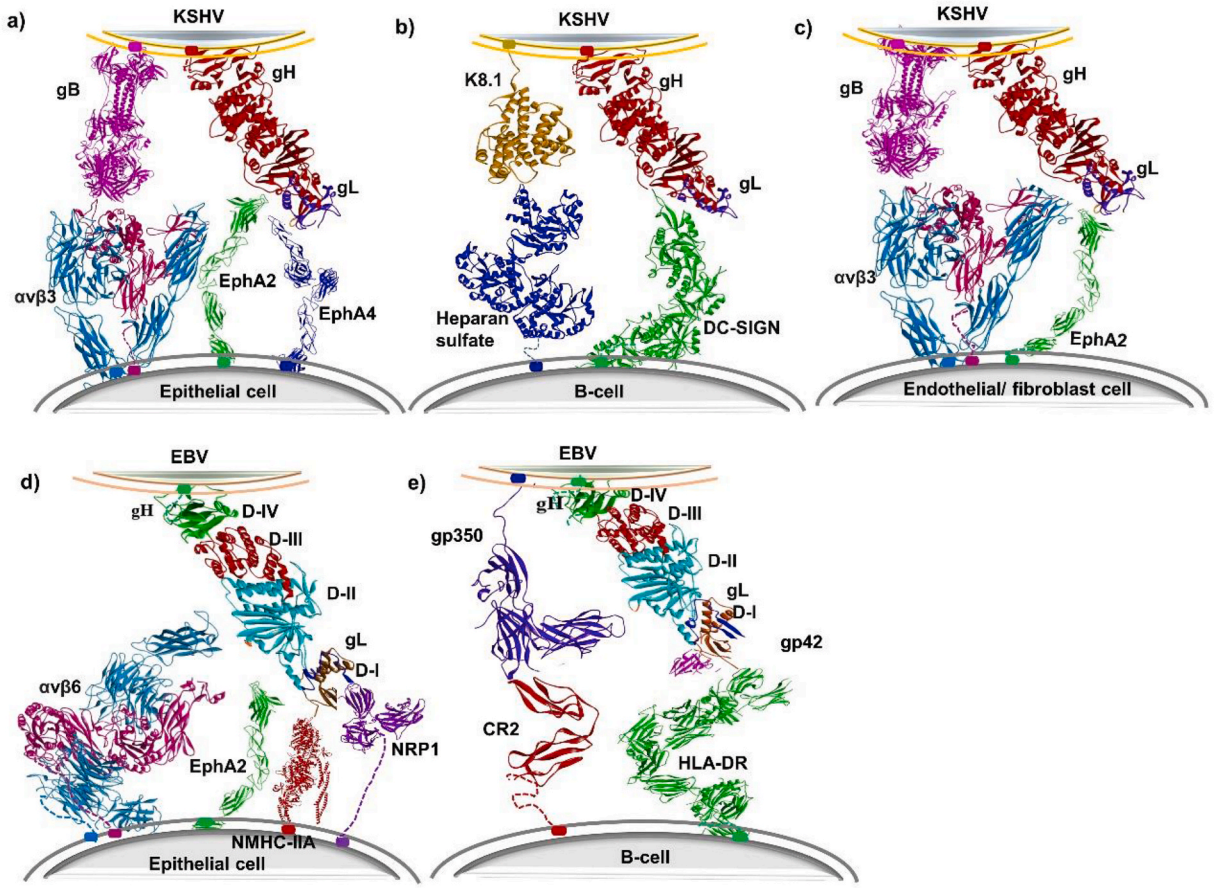

Fig. 2. Human γ-herpesviruses attachment to different cells. **a)** KSHV gHgL and gB (modelled structures) make an attachment with epithelial cell via integrin (αVβ3; Pdb Id: 1JV2) and EphA2 (Pdb Id: 2X10) and -A4 (Pdb Id: 4BK4) **b)** KSHV gHgL and K8.1 (Pdb Id: 5ZB1) make an attachment with heparan sulfate (Pdb Id: 1VKJ) and DC-SIGN (Pdb Id: 6GHV) receptor in B-cell **c)** KSHV (gHgL and gB) attach with endothelial and fibroblast cells via integrins and EphA2 **d)** EBV gHgL (Pdb Id: 3PHF) attaches to epithelial cell receptors EphA2, integrins (αVβ6; Pdb Id: 4UM8), NRP1 (Pdb Id: 2QQM) and NMHC-IIA (Pdb Id: 4PD3) **e)** EBV (gp350; Pdb Id: 2H6O, gHgL; Pdb Id: 3PHF and gp42; Pdb Id: 5T1D) attachment to B-cell receptors CR2 (Pdb Id: 1LY2) and HLA-DR (Pdb Id: 2WBJ).

(E1D1) is known to inhibit epithelial and B-cell fusion of EBV selectively [57]. The EBV soluble form of truncated gHgL (gHtgL) can bind specifically with epithelial cells but not with B cells. Concurrently, a gH ablated virus is able to use gp350 potentially to bind with the ectopically expressed CR2-positive epithelial cells and it lacks its binding ability to CR2-negative cells [5]. Moreover, mutagenesis studies identified several gHgL mutations that decreased epithelial cell binding and fusion while the B cell was unaltered, indicating that gHgL is an important determinant for EBV cell tropism [58]. There are different regions of EBV gHgL that participate in B- and epithelial cell entry [58]. The E1D1 epitope mutations in gL showed that this region of gHgL is important for cell-specific roles in epithelial cells instead of B-cells entry. The C-terminal domain (CTD) of gp42 showed interactions with the gH lysine-glycine-aspartic acid (KGD) motif which explains the ability of gp42 to block the epithelial-cell entry. Intriguingly, the region does not interact with this KGD motif. Thus, it implicated that the C-terminal of gp42 interacted with an additional gHgL region and altered epithelial-cell entry [57].

The EBV-gH has 4 domains. Domain-I (D-I) (1–65 amino acids) interacts with gL which acts as a molecular chaperone. The rest of the gH (66–672 amino acids) folds into three sequential globular domains (D-II, D-III and D-IV) [38,59]. The gH D-II disulfide bond mutants and 8 amino acid (698–706) mutation study at the CTD revealed the importance of gH in the attachment and fusion of EBV with the epithelial cells [60,61]. Further, the crystal structure of gHgL (KSHV) was predicted based on the structural specifications of EBV gHgL. KSHV gH is also divided into four domains from N-terminus to C-terminus; D-I (A22-I87), D-II (R88-N365), D-III (H366–I552), and D-IV (P553-A703). The gB is synthesized in a precursor form of 110 kDa polypeptide which further produces disulfide-linked full-grown polypeptides of molecular weight 75 and 54 kDa after proteolytic cleavage [62]. The gH and gL of KSHV and EBV share five and two disulfide bonds, respectively [63]. Also, the gHgL complex of KSHV and EBV is known to bind with different epithelial cell receptors. Few host receptors are common in both KSHV and EBV such as integrins and Eph receptors. Heparan sulfate (HS), glutamate/cystine exchange transporter (X-CT), and dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) receptors are known to use by KSHV whilst EBV uses neuropilin1 (NRP1) and non-muscle myosin heavy chain IIA (NMHC-IIA) for epithelial cell entry (Fig. 2) [4,5,64–66].

1.2. Role of Eph receptors for γ-herpesviruses entry into epithelial cells

Recently, EphA2 was identified as a specific host entry receptor for EBV [67]. The EBV gHgL is known to make a complex with ligand-binding domain (LBD) region of Eph receptor to gain entry into the epithelial cells (Fig. 2) [32]. EBV gHgL binds to the peripheral region of LBD primarily by using gL [63]. EphA2 has also been evaluated as one of the six highly expressed plasma membrane proteins in epidermal growth factor (EGF)-induced nasopharyngeal epithelial cells (NPECs) and EBV is a well-known cause of nasopharyngeal carcinoma [51]. An RNAi and knockout analysis of EphA2 showed reduced EBV epithelial cell fusion and infection by 90% and 80%, respectively [51]. A similar study also revealed that EphA2 gene knockout in HEK293T cells reduced EBV infection up to 85% [50,70]. Also, the overexpression of EphA2 increased EBV infection in epithelial cells [50]. Moreover, the intracellular kinase domain of EphA2 was reported to be dispensable for EBV infection [67]. Several mutational studies also added up to the investigation of entry mechanisms of these viruses [58]. The gL mutant (N69L/S71V) study of EBV showed a higher binding affinity for EphA2 compared to the wild type. It was evaluated that this glycosylation site (N69/S71) possibly offered steric hindrance in the wild type interaction scenario [68].

Yet another γ-herpesvirus, i.e., KSHV uses gHgL and gB to fasten with EphA2 molecules in epithelial, endothelial and fibroblasts cells. EphA2 has a crucial role in the KSHV infection of endothelial cells, and its interaction has been shown through co-precipitation with KSHV gHgL protein complex [69]. The gHgL analysis has revealed the regions of gH that are essential for gL and EphA2 binding [39]. Mutations in gH ELEFN motif (Glu-Leu-Glu-Phe-Asn$^{50\text{-}54}$) results in decreased interaction with EphA2 but not with gL [39]. Thus, the KSHV gH (ELEFN$^{50\text{-}54}$) motif is important for KSHV fusion. Contrarily, EBV gHgL is deprived of this domain, so, it is likely that EBV gHgL utilizes some other domain for the fusion activity [68]. In contrast, for establishing the attachment with B-cell, KSHV glycoprotein K8.1 and gHgL uses receptors like HS and DC-SIGN [62]. The primary attachments of the virus trigger the downstream cascading factors in the host cells and eventually results in macropinocytosis or clathrin-dependent endocytosis (CME) in epithelial cells [69]. An *in-silico* report suggested that KSHV gHgL made more contacts i.e., numerous hydrogen bond interactions with EphA2 than EBV which indicated stronger binding of KSHV glycoproteins with EphA2 [63]. The antibodies and siRNAs directed against EphA2 resulted in reduced KSHV infection in lymphatic endothelial cells. EphA2 blocking in endothelial cells with a polyclonal antibody result in a substantial reduction of KSHV infection [69,70]. Therefore, the Eph receptor is an attractive target for tackling KSHV infection [71]. Once KSHV makes an attachment to Eph (EphA2 and -A4); c-Cbl E3 ubiquitin ligase participates in KSHV entry through polyubiquitination of EphA2 at K63 which is necessary for effective internalization (Fig. 3) [70,71]. EphA2 knockdown and mutations in the tyrosine kinase domain (TKD) or sterile alpha motif (SAM) domains significantly reduces the signal inductions, virus internalization and gene expression [71]. The essential role c-Cbl was also checked in KSHV infection by knocking down the c-Cbl. The c-Cbl plays an essential role in clathrin-mediated endocytosis (Fig. 3). The c-Cbl knockdown abolished the polyubiquitination of EphA2 and eventually the association with clathrin protein [71]. The PI3K also regulates herpesviruses phagocytosis coupled pathways which could be an important mechanism for virus entry into host cells [71–73].

Apart from EphA2, several other Eph molecules (i.e., EphA4) expressed on epithelial cells can be used by KSHV as an attachment and entry factor (Table 2). Single and double knockout studies of EphA2 and -A4 unveil that both these receptors play a role in KSHV fusion and subsequently the entry into the host cells [74]. Furthermore, KSHV also utilizes EphA7 molecules for cell-to-cell transmission such as epithelial to B-cells (i.e., iSLK to BJAB cells). The knockout of EphA7 showed a reduction in KSHV transmission into BJAB target cells up to 76% [75]. Besides, in EBV infections only EphA2 is being revealed till date. Also, studies have mentioned the aggravated response of EBV co-infection with other pathogens. EBV infection along with a bacterium (*H. pylori)* showed enhanced levels of EphB6 in gastric epithelial cell lines which eventually contribute to cancer progression [35]. Thus, it is suggesting the involvement of other Eph family members in EBV infection and eventually in pathologies. Further, the exact binding interaction of EBV gHgL with EphA2 is yet to be determined through various techniques like electron microscope (EM) or cryo-EM. Moreover, the comparative studies of EBV epithelial and B cell triggering complexes may shed light on how EBV glycoproteins orchestrate these two cell types to gain entry and establish a successful infection.

1.3. Other epithelial cell receptors for γ-herpesviruses entry

Heparan sulfate (HS): Along with Eph receptors, KSHV is also known to utilise HS as an attachment molecule and modulates the natural host cell signal pathways (Fig. 3) [76]. KSHV gB plays a key role in the initial virus and host cell interaction by binding to cell surface receptors (i.e., HS) accompanied with integrins [77]. gB interaction triggers the activation of signalling molecules such as FAK, Src, PI3–K, and Ras homologous-guanosine triphosphatase (Rho-GTPase) [71]. The pre-treatment of soluble heparan revealed dose-dependent inhibition of KSHV binding and signalling in human foreskin fibroblast (HFF) cells [78]. An *in vitro* study showed that gB bound specifically with HS, but not with other glycosaminoglycans (GSGs) such as chondroitin sulfates,

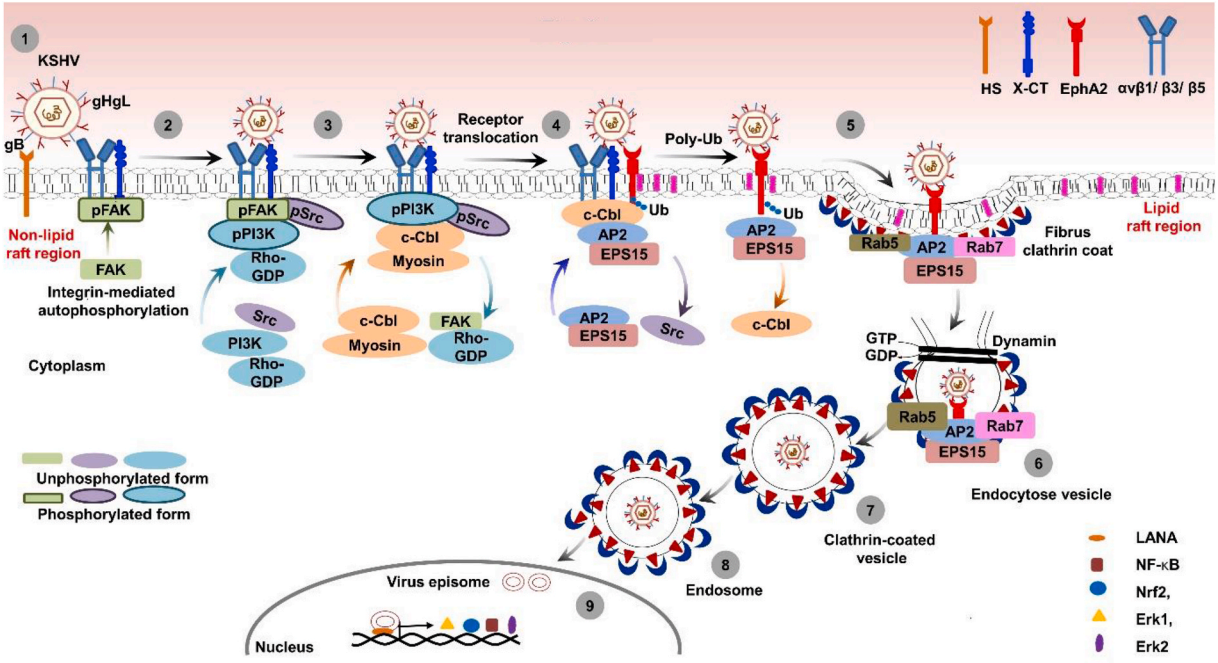

Fig. 3. Possible mechanism of KSHV entry into the epithelial cell. **1)** KSHV infection is initiated by binding to the cell surface proteoglycans HS. **2&3)** Temporal association of HS subsequently followed by interaction with integrins (αvβ1, αvβ3, αvβ5) and X-CT molecules in the non-lipid raft (NLR) parts of the membranes. KSHV interactions with integrins and trigger autophosphorylation of FAK at tyrosine 397, which creates a binding site for the SH2 domain-containing Src family kinases and subsequently leads to the activation of PI3–K and Rho-GTPases and further is recruited c-Cbl. **4)** c-Cbl mediates a rapid selective translocation of KSHV into the lipid rafts (LR) along with the integrin (except αvβ5) and xCT receptors to the Eph molecule. **5)** c-Cbl ubiquitinate the Eph receptor and recruit AP2 and Eps15, and triggers the assembly of clathrin-coated pits. **6)** Clathrin-mediated endocytosis and form vesicle with the help of dynamin protein. **7)** Complete clathrin-coated vesicle forms 8) Release of virus particle from the endosome. **9)** KSHV replicate into the nucleus and modulate genes expression of NF-κB, Nrf2, Erk1 and Erk2.

Table 2
Enlistment of Ephs and ephrins expressed by different human cells.

Cell types	Ephrin's	Eph's	References
Endothelial	A1, -B1, and -B2	A2, -B2, and -B4	[24,139]
Intestinal epithelium	All A's, and B1–B3	A1-A3, A5-A8, B1–B4, and -B6	[24]
Neuron	A5	A4, -A5, -A6, and -B2,	[19,147]
Microglia	B2, -A3 and -A4	B1 and -B2	[148–151]
Astrocyte	A3, -A5, -B1, and -B2	A2, A4, -B2, and -B4	[9,145,149, 152–154]
Oligodendrocyte	A1, -A5, -B1, -B2, and -B3	A2, -A4, -B1, and -B2	[11]
Leucocytes		A1, -A3 and -A4	[148]
T-lymphocytes	A1, -B1, and -B3	A1-A4, -A7, -A8, -B1, -B2, -B3, and -B6	[148]
B-lymphocytes	A4	A1-A4, -A8, -B2 and -B4	[148]

N-acetyl heparan, and de-N-sulfated heparan. Similarly, the pre-treatment with chondroitin sulfate A and C have not averted the infection of KSHV which suggests HS specificity with KSHV [78]. HS involvement in the KSHV host cell infectivity has also been demonstrated in various primary B-cells and B-cell lines with defective HS biosynthesis. Studies related to KSHV and EBV negative BJAB cells showed that the expression of HS made the host cells more prone to KSHV infection. Similarly, KSHV failed to infect the HS ablated BJAB cells [79]. Using gB, gpK8.1A, complement control protein (KCP) or ORF4, and gH, KSHV makes attachment with HS and subsequently facilitates virus infection [75]. Furthermore, the biochemical evaluation revealed the presence of heparin-binding domains (HBD) in KSHV proteins and the gB extracellular domain possesses HBD with a conserved sequence of 108–117 amino acids (HIFKVRRYRK). KSHV gpK8.1A has atypical HBDs whilst gH lacks the HBD's [78,80]. The recombinant and purified forms of KSHV gB and gpK8.1A bind specifically with HS through heparin-agarose and molecules regardless of lower affinity towards chondroitin sulphates [81,82]. Similarly, the envelope proteins such as gC, gB, gD of HSV-1/HSV-2 and gB protein of VZV make an attachment with heparan sulfate for getting access into the host cells. The gB & gM of CMV and gB & gp65 of HHV7 also has the properties to establish interaction with HS [83]. Till to date, no report has claimed HS usage by EBV which suggests that may be due to EBV envelope glycoproteins lacking HBD.

Integrins: KSHV was evaluated as the first herpesvirus to make an attachment with integrins and use it as an entry receptor in the adherent cells [84]. gB of KSHV possesses (amino acid 27–29) a typical integrin-binding motif Arg-Gly-Asp (RGD) like many integrin-binding extracellular matrix (ECM) proteins [85]. The pre-treatment with anti-RGD antibodies and soluble RGD peptides (i.e., RGDgBN-1; RGDTFQTSSSPTPPGSSS) to HMVEC-d (human microvascular dermal endothelial cells) and HFF cells showed a significant reduction in KSHV infectivity [85]. Functional blocking of α3β1 integrin showed reduction in KSHV infection up to 30–50%, whereas the overexpression of α3 integrin (form complex with β1 integrin) in Chinese hamster ovary (CHO) cells increased the KSHV infectivity [85]. Though, CHO cells are not the natural target cells of KSHV. Also, some inconsistencies are there regarding the use of different integrin subtypes by KSHV for tropism. For instance, a study on 293-T cell line was unable to evaluate the blockage or reduction in the KSHV infection after treating the cells with soluble α3β1 [86]. Further, studies have also highlighted the key role of integrin localization in the lipid raft and lipid non-raft region on the cell surface as an important criterion for KSHV infection [87]. KSHV attachment to αv integrins in the non-lipid raft region triggers autophosphorylation of focal adhesion kinase (FAK) and assembly of other molecules such as Src, Rho-GTPase phosphoinositide 3-kinase (PI3K), c-Casitas B-lineage Lymphoma (c-Cbl) ubiquitin ligase (Fig. 3). Though the gB is highly conserved among herpesviruses, still only HHV-8 gB contains the RGD motif. The FAK autophosphorylation (Tyr397) instigates by the HHV-8

gB interactions with integrins and fabricate a binding site for the SH2 domain of Src family kinases. The activated Src phosphorylates in turn activate the RhoA and Cdc42 Rho GTPases through phosphorylation of p85 of PI-3K [71]. Further, the receptor translocates into the lipid-raft region where it makes an attachment with EphA2 which eventually triggers the recruitment of adaptor protein 2 (AP2) and epidermal growth factor receptor substrate (Eps15) [47,71] (Fig. 3). FAK molecule is activated by growth factors through integrin molecules and functions as a receptor-proximal regulator of cell motility.

Likewise, the D-II region KGDXXXL of EBV-gH is known to interact with αv integrins (Fig. 2). The soluble integrin and the natural ligands of integrins such as fibronectin and vitronectin are able to reduce EBV binding and the infection partially into epithelial cells [5]. In epithelial cells, integrins act as both an attachment and fusion entity for EBV, although their vital role is likely to be in the fusion process [5]. Further, αvβ6 and αvβ8 soluble forms triggered the epithelial cell fusion through EBV gB and gHgL. Another EBV envelope protein, BMRF2, is also involved in the EBV entry into epithelial cells through the β1 family of integrins [88]. Chesnokova et al. revealed that gHgL binding affinity to epithelial cells increased thrice of its magnitude in the presence of Mn^{2+} [5]. The EBV binding and infection was found to be significantly reduced after treatment with gH 13 amino acid KGDE peptide. The down-regulating of the αv integrins also corresponds to reduced EBV infectivity [5]. In contrast, the knockout of αv integrins in HEK293 cells showed no difference between wild type HEK293 and αv integrin knockout HEK293 cells for EBV infection and fusion activity. It indicated that αvβ5, αvβ6 and αvβ8 integrins are tie-up receptors but not the preliminary receptors for EBV entry in HEK293 cells [59,67]. Moreover, EBV and KSHV are not the only herpesviruses that carry potential integrin-binding motifs in gH. Alpha-herpesvirus such as HSV, gH homolog (803 aa) also consists of an RGD motif at residues 176–178 [5]. Instead, the fusion of HSV resembles closely to EBV with B-cell utilising gB and gHgL with gD which is a functional analogous to gp42 [5].

X-CT: It is a 12-transmembrane glutamate/cystine exchange transporter, and plays a role as a fusion-entry receptor for KSHV [89]. X-CT is known to form a complex with a 125 kDa protein CD98 which forms a disulfide-bonded heterodimeric complex on the cell surface [89,90]. CD98, first identified as an integrin α3 associated molecule, is known to regulate the transport of amino acids, cell fusion, proliferation, and adhesion [62]. In the HMVEC-d cells, X-CT protein assembles into a multimolecular signalling complex during KSHV micropinocytosis [91]. It is highly plausible that X-CT can direct downstream signalling to ease the endocytic process of KSHV entry. Interaction of X-CT with integrins triggers the signalling process, although an additional exploration is needed [92]. Yet, the pre-treatment of the heparin and soluble α3β1 integrin inhibits α3β1-CD98/X-CT complex formation. The α3β1-CD98/X-CT complex played a key role in KSHV initial binding with the HS. After HS interaction, KSHV establishes interaction with integrin and leads to possible conformational changes in envelope glycoproteins [77]. Further, the glutamate/cystine transporter role in the case of other herpesviruses entry is still less explored.

DC-SIGN: It is typically expressed on the surface of myeloid dendritic cells (DCs), and a C-type lectin. DC-SIGN is known to be utilised as a receptor by many viruses such as sindbis virus (SINV), human immunodeficiency virus (HIV), herpesviruses (i.e., KSHV) and bunyaviruses [93,94]. During the establishment of infection, KSHV utilizes DC-SIGN to enter into human DCs, macrophages and activated B cells [84]. The anti-DC-SIGN monoclonal antibody and soluble DC-SIGN peptide treatment hinder KSHV binding and eventually the infection [77]. Clearly, high expression of DC-SIGN on B cells make it more prone to KSHV infection [46]. The treatment with anti-DC-SIGN monoclonal antibodies revealed partial blocking of KSHV which points towards the presence of additional binding receptors namely HS and other co-receptors [48]. Besides, the gB of KSHV possessed high mannose sugar modified residues which are reported to bind with DC-SIGN and facilitate KSHV entry [48]. Along with KSHV, DC-SIGN facilitates interaction with wide range of pathogens including bacteria (*H. pylori*), viruses (HIV-1, Ebola, CMV, HCV, Dengue and SARS-CoV) and parasites (*Leishmania pifanoi*) [95]. So far, no study is being conducted on the evaluation of whether DC-SIGN acts as an EBV entry receptor. Although, EBV has been observed to infect DC-SIGN positive cells such as immature DCs, monocytes and some macrophages. Xu et al., also speculated that immature DCs express DC-SIGN receptors which probably recognize EBV- secretory IgA (SIgA) complex [95].

NRP: In different cell types, the NRP1 has multiple functions and has a specific role in signalling by escalating the activity of RTKs, acting as a co-receptor for class III semaphorins and various growth factors [96]. Various growth factors and signalling molecules bind to NRPs through a carboxy C-terminal basic sequence motif (C-end Rule or CendR motif). NRP1 is also known to bind with the CendR motif containing peptides, which has a consensus sequence R/K/XXR/K for internalization [97]. This cleavage motif is also possessed by the gB of EBV which is highly conserved in the herpesvirus family. The cleavage motif is recognized by the cellular protease furin and it can be a potential cryptic C-end Rule (CendR) motif [59]. Treatment with soluble NRP1 or the knockdown of NRP1 reduced EBV infection to about 50% in NPECs. Likewise, NRP1 overexpression significantly increased the EBV infection efficiency. Moreover, the role of NRP2 was found to be opposite to that of NRP1 [66]. Thus, it led to the speculation that NRP1 can serve as an entry factor for EBV and make an attachment with interacting partner gB. *In vitro* binding assay of gB with NRP1 revealed EBV gB 23–431 established direct interaction with NRP1. Similarly, gB (23-427) CendR motif deletion mutant revealed a reduction in the NRP1 interaction with gB [66]. The analysis also showed that several other deletions in gB like gB 23–88 and gB 428–431 abolished the interaction between NRP1 and gB which indicated the key role of these regions [66]. NRPs also have a role in other herpesvirus entries such as HCMV use NRP2 protein to get access into epithelial and endothelial cells [98]. HCMV pentamer (gH/gL/UL128/UL130/UL131A) make interaction with the NRP2 molecule which was speculated when pentamer-specific HCMV antibodies block NRP2 binding [98]. NRP1 also acts as a receptor for SARS-CoV-2 as it binds to furin cleaved substrates and is abundantly expressed in respiratory and olfactory epithelium [99].

NMHC-IIA: The 250 kDa NMHC-IIA is an actin-binding protein having the properties of actin cross-linking and contraction which is regulated by the light and heavy chains phosphorylation [100]. The NMHC-IIA played an important role in many viruses' infection including the porcine reproductive and respiratory syndrome virus, thrombocytopenia syndrome virus and herpesviruses [65]. Although, it is mainly located in the cell cytoplasm [59,64]. The membrane fractionation discloses the aggregated NMHC-IIA with EBV gHgL in apical surfaces of SLCs (NPECs grown as sphere-like cells) [59]. NMHC-IIA was identified as a gHgL binding protein and played an important role in enhancing the EBV infection. It was evaluated by a myc-tagged gHgL pull-down assay and co-immunoprecipitation [59,64]. The knockdown and blocking (with antibody) of NMHC-IIA resulted in the reduced EBV binding and SLC infection, but no change was observed in adenovirus infection [59,64]. In contrast, the cytoplasmic overexpression of NMHC-IIA was not able to increase the EBV infection. The EBV infection was increased only when NMHC-IIA was redistributed to the cell membrane [64]. Thus, the efficiency of EBV infection increased due to cell surface localization of NMHC-IIA and gHgL. However, the mechanism of NMHC-IIA redistribution is yet to be explored. HSV-1 was also known to use NMHC-IIA as an entry co-receptor [101]. Further, no reports have suggested NMHC-IIA as KSHV entry receptor.

1.4. Association of KSHV and EBV infection with various diseases

Cancer: KSHV is known to cause Kaposi sarcoma (KS) prominently in AIDS patients [102]. It is also associated with other B-cell malignancies like primary effusion lymphoma (PEL), a plasmablastic variant of multicentric Castleman's disease (MCD) and virus influenced

inflammatory cytokine syndrome (KICS) [102–104]. In contrast, EBV was discovered from Burkitt lymphoma (BL) cells in 1964 by a young pathologists, Anthony Epstein and Denis Burkitt [105]. EBV is widely associated with infectious mononucleosis, malignancies associated with B-cells, epithelial cells and several neuronal disorders [33,34,104,106,107]. Approximately 95% of the adult human population is EBV positive although the majority of them remain asymptomatic [108]. Several studies showed that the RTKs such as Eph, epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) play important roles in EBV-association with cancer [32,109,110]. In EBV-associated epithelial cancers, Eph (i.e., EphA2) expression was found to be significantly higher in EBV-positive nasopharyngeal carcinoma cells (NPC) than in EBV-negative NPC [111]. EBV association with several disorders leads to predict that EBNA-1 and other EBV proteins (i.e., EBNA-3C) alter the gene expression of tumour suppressor genes and apoptotic pathways which results in cancer and other pathologies [112–117]. Often EBNA-1 protein is associated with endemic BL. BL is a B-cell non-Hodgkin's lymphoma, and the exact mechanism underlying EBV and B-cell malignancy are still elusive. Also, there is a strong association between Hodgkin's lymphoma (HL) and EBV infection and almost 40% of HL tumours have shown the presence of EBV [118]. Compared to epithelial cells, B-cell lymphoma cell lines (Akata and Raji) observed undetectable EphA2 expression. Thus, these findings demonstrated that EphA2 is essential for EBV infection of epithelial cells [51]. EBV mediated EphA2 signalling promoted tumour metastasis by inducing vasculogenic mimicry (VM) formation during gastric tumorigenesis [119,120]. The VM is also induced by EBV latent membrane protein-2A (LMP-2A) through activation of PI3K/AKT/mTOR/HIF-1α (hypoxia-inducible factor-1α) signalling cascade in epithelial cancer cells. Both xenografts and clinical samples of NPC and EBV-associated gastric carcinoma (EBVaGC) exhibit VM. VM is histologically also correlated with the activation of PI3K/Akt and HIF-1α factors [111].

Furthermore, the EBV positive biopsies of diffuse large B-cell lymphoma (DLBCL) showed lower expression levels of EphA4 compared to the EBV negative biopsies. It was further verified by the inverse correlation of EphA4 and EBV infection in DLBCL patients [41]. Patients with EBV positive DLBCL have difficult overall survival and progression-free survival relative to their EBV negative counterparts, yet the detailed mechanism has not been completely understood. Also, some EphA4 ligands, such as ephrin-A1, A2, A3, A4, and B1 were found to be down-regulated post-EBV infection [41].

Similarly, KSHV triggers these malignancies by altering the function of several receptor proteins (i.e., integrins, IGFs, CXCR chemokine receptors) and kinases [i.e., Eph, FAK, extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MAPK)]. Among these kinases, Eph is one such molecule that sets off KSHV signalling, entry, and infection in epithelial, endothelial, fibroblast and B-cells [70]. Upon binding of KSHV with the Eph family receptors, particularly EphA2, several oncogenic factors like FAK, Src and PI3–K are triggered [51,70]. Eph expression in different tumours revealed that EphA2 is overexpressed in 61% of Glioblastoma (GBM), 76% of ovarian cancers, 60–80% of breast cancer and 85% of prostate adenocarcinomas [70,121,122]. Also, erythroblastic oncogene B2 (ErbB2) and EphA2 interaction amplified rat sarcoma oncogene/extracellular receptor kinase (Ras/Erk) signalling and Rho-GTPase activation, likely contributing to the increased proliferation and motility of EphA2-expressing tumour cells [123]. KSHV has pleiotropic effects on cell signalling which could contribute to oncogenesis and angiogenesis, the hallmarks of cancer. In KSHV infected cells, the PI3K/Akt/mTOR (mammalian target of rapamycin) pathway is highly upregulated which promotes survival and growth of the cells [124]. The PI3K/Akt/mTOR pathway is mediated by several KSHV genes, such as viral Fas-associated death domain-like interleukin-1β-converting enzyme-inhibitory protein (vFLIP), kaposin B and a KSHV G protein-coupled receptor (vGPCR) [125]. KSHV protein vFLIP stimulates activation of nuclear factor kappa B (NF-kB) whereas latency-associated nuclear antigen (LANA), inhibits p53 in KS, MCD and PEL [107,126,127]. KSHV may trigger and influence a disorder either alone or in combination with other herpesviruses [128,129]. For example; PEL, a rare, high-grade non-Hodgkin's lymphoma is associated with the presence of KSHV. Importantly in most cases, the EBV coinfection with KSHV was included in PEL, although the role of EBV in the pathogenesis of the tumour is still not clear [129]. The variations in the EphA2 gene also affect the susceptibility of KSHV infection and its association with KS development in a South African HIV-infected patient's cohort [130]. In addition to EphA2, other Ephs such as EphA4 altered not only the cell phenotype but also the signalling mechanisms in human glioma U251 cells [130,131]. EphA4 formed a receptor complex with fibroblast growth factor receptor 1 (FGFR1) which is known as the EphA4-FGFR1 complex. This complex further potentially advanced the FGF2-mediated cell proliferation and migration accompanied by the enhancement of Akt and MAPK phosphorylation. The Rac1 and Cdc42 were also found in the EphA4-overexpressing cells [131].

Neurological complications: Several herpesviruses including EBV have a role in fabricating the neurological complications. For decades the connection of EBV with encephalitis, meningitis, multiple sclerosis, Alzheimer's diseases and optic neuritis have been foregrounded [67,132,133]. EBV infection was detected in B- and plasma cells inside the brain which is nearly 100% of multiple sclerosis (MS) cases examined, whereas it is not the case in other inflammation-mediated brain diseases [134]. Therefore, the exact mechanism of EBV association with the brain disorders is again a deeply fascinating question. There are different modes of EBV pathogenesis have been speculated: **i)** EBV may directly infiltrate the nervous system (NS). Most children with EBV viral encephalitis were not having any infection symptoms outside the brain like tonsillitis and enlarged lymph nodes. This suggested a primary neurological infection of EBV [135,136] **ii)** EBV potentially triggered immune-mediated symptoms in the NS. EBV may share a common antigen (molecular mimicry) with the myelin glycoprotein of oligodendrocytes. Molecular mimicry induces the immune system to produce autoimmune T lymphocytes as well as anti-neuronal antibodies against the autoantigens [137,138] **iii)** EBV reactivation from latency could trigger pathogenic features of neuronal disorders, especially in immunosuppressed patients [139]. Furthermore, there are no reports which claim KSHV connection with neural diseases. HSV, VZV, CMV, HHV-6 are also neurotropic viruses and a common cause for serious acute and chronic neurological disease of the central nervous system (CNS) [135].

Different brain cells express different EBV entry receptors such as Ephs, ephrins, integrins and NRP's. Eph and ephrin molecules are highly expressed in the developing brain and play a key role in setting up neuronal connections by giving signals to axons. Eph receptors also mediate the formation of synaptic connections [140]. Upregulation of multiple Eph receptors and ephrins have been detected in nervous system injury and various complications [141]. For instance, after spinal cord injury EphA3, -A4, -A6, and -A8, -B2, -B3, and ephrin-B2 expression were increased which is associated with the lack of axonal regeneration [142–145]. Studies also highlighted the connection of Eph receptors with the EBV entry mechanism [67]. Thus, it led us to hypothesize a strong possible connection of EBV entry and infection into brain cells leading to various neurological disorders (Table 2).

EBV may aid in the brain inflammatory reactions through the infiltration of peripheral blood mononuclear cells (PBMCs). The aforementioned report has checked EBV mediated changes in the glial cells (U-87 MG) through direct infection, by supplementing glial cells with EBV-infected PBMCs and finally with PBMCs conditioned supernatant [34]. It showed an enhanced expression of IL-6 in case of direct infection and supernatant treated cells. Further, the NF-κB level was also found to be reduced in cells upon direct EBV infection [34]. Yet, another study showed that the EBV $^{+}$ lymphoma cell line showed an epigenetic switch is implementing a neuroinvasive phenotype with upregulation of SPP1/Osteopontin. The epigenetic modification triggers B-cell trafficking to the CNS and it can provide a new path to study B-cell

neuro-invasion and eventually it is associated with CNS lymphoma and brain autoimmune disease including multiple sclerosis (MS) [146]. Furthermore, the biomolecular nuances in human glial cells (i.e., HMC-3 and U-87 MG) were evaluated by Raman spectroscopy after EBV infection in a temporal manner. In the microglial cells, an increase in the DNA activity was found at 2 hpi (hour's post-infection) which is accompanied by the increased signals for PIP or lipid molecules indicating the enhancement in the signalling processes throughout the cell. It is suggested that EBV after entering into the nucleus of microglia during 6–12 hpi, virus facilitates its replication cycle by steering the nuclear metabolism of glycogen and amino acids. Notably, abnormal glucose metabolism is commonly correlated with various neuro-inflammatory disorders (i.e., MS) [33]. Nevertheless, in the microglial cells at 6 to 12 hpi, most biomolecules at the periphery were downregulated (except some polysaccharides and amino acids). In contrast, in the astroglial cells, the expression of various molecules such as triglycerides, fatty acids, lipids, and proteins was observed at 6–12 hpi which was speculated as the processing of the virus inside the nucleus. The processes altered in a host cell due to EBV entry or manipulation in the nuclear milieu of microglial and astroglia cells occurred approximately after 6 hpi and 4 hpi, respectively [33].

2. Therapeutic targets

Since Eph and ephrins have a remarkable role in infectious diseases it has been increasingly recognized as an attractive therapeutic target for many diseases which includes anticancer therapeutics, synaptic plasticity modulators, homeostasis of bone, and the stem cell biology [21,116,155]. Most of the kinase inhibitors possess poor selectivity and target multiple kinases. So, the small antagonist molecules proved as effective suited molecules for blocking the ATP-binding pocket in the Eph kinase domain [156]. Dasatinib, a potential kinase inhibitor, is reported to inhibit Eph receptors [157]. It also inhibits kinase-independent EphA2 oncogenic signalling in cells through an indirect mechanism [157]. In this regard, the EphA2 soluble peptides, antibodies, and inhibitors such as 2,5-dimethylpyrrolyl benzoic acid against EphA2 may efficiently block the viral (EBV and KSHV) entry into the cells [51]. Further, with high selectivity and binding affinity, several short peptides proved to be a likely way for modulating Eph-ephrin signalling. A series of do-decapeptides selectively target the ephrin-binding pocket of Eph receptors and antagonize ephrin binding [156]. For instance; KYL peptide (KYLPYWPVLSSL) profoundly targeted EphA4 expressed in the brain cells [158]. The YSA agonistic peptide (YSAYPDSVPMMS) specific to EphA2 and its conjugation with paclitaxel, increased its efficacy to target the cells [159]. Along with these peptides, there are antibodies conjugated with drugs, toxins, radioisotopes, and nanoparticles that enhance the targeted delivery to tumour tissues overexpressing the Eph receptor or ephrin [160,161]. Antibodies such as 1C1 (EphA2 antagonist) conjugated with microtubule-disrupting drugs showed efficacy against epithelial cell tumour xenografts [162]. Notably, the 1C1 was conjugated with a highly toxic microtubule-disrupting drug (MEDI-547) and it showed anti-tumour activity [163]. The phase I clinical trial of MEDI-547 conjugated 1C1 antibody at a sub-therapeutic dose caused adverse events, including bleeding and coagulation, resulting in premature termination of the trial [164]. Thus, the chronic treatment with these molecules has side effects and toxicities. After multiple rounds of screening of Eph kinase inhibitors some showed promising results (i.e., bosutinib); the preclinical studies on mice showed their usefulness for inhibition of angiogenesis, treatment of diabetes and other diseases [21].

Alternatively, few compounds were used in clinical trials for the treatment of EBV, KSHV, HSV-1, HSV-2 and VZV infections [165,166]. Several antiviral agents like acyclovir, valacyclovir, penciclovir, and famciclovir are used against herpesviruses to restrict their progression into the host cells [165,167]. Furthermore, the emerging therapies of B-cell depletion, particularly anti-CD20 agents such as rituximab, ocrelizumab, and ofatumumab showed promising clinical benefits [168]. Additionally, there are several anti-gHgL monoclonal antibodies that target different regions of gHgL that might block fusion; CL40, CL59, E1D1 and AMMO1 [57,169,170]. Together with these observations, a monoclonal antibody to gHgL blocked virus binding to a CR2-negative as well as CR2-positive cell [5]. This suggests that Eph molecules might serve as the missing co-receptor needed to trigger epithelial cell fusion by EBV glycoproteins. Furthermore, no specific anti-EBV FDA approved drug is available, to date. Recently, an *in-silico* study showed that natural compounds like bruceantin and EGCG could stably interact with gH at functionally relevant sites. *In-silico* mutational analysis of the V265, L269, L315, I423, I459, L474 and F475 amino acids showed their involvement in stable binding with gH protein [171].

3. Conclusion

The γ-herpesvirus attachment and entry specifically into the epithelial cells are poorly explored. Several receptors like integrins, Eph receptors are known to be involved in the process directly or indirectly. The gHgL and gB of KSHV make an attachment with epithelial cell receptors like HS, integrins and Ephs and eventually activate certain cellular downstream molecules such as FAK, PI3K, Src and c-Cbl. The detailed mechanism of EBV entry into the epithelial cell needs in-depth investigations. Besides, studies showed that knockdown of these Eph receptors mitigate the EBV infection, and the Ephs overexpression has the potential to restore the infection. Further, certain EBV proteins (gHgL) mutational studies have also evaluated the role of Eph receptors in viral entry. Therefore, it is suggested that these receptors are vitally contributing to the γ-herpesvirus entry. The viral blocking at the entry point could negate the virus-induced stress induced into the cell. Thus, these entry receptors may prove to be elegant drug targets for therapeutics development.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors contribution

Annu Rani- Conceptualization, data curation, original draft writing, figure and table preparation; **Shweta Jakhmola**- Conceptualization, critical review and editing; **Dr. Srikanth Karnati**- Critical review and editing; **Dr. Hamendra Singh Parmar**- Critical review and editing; **Dr Hem Chandra Jha**- Conceptualization, critical review and editing. All authors read and approved the manuscript.

Acknowledgements

We thank the Council of Scientific and Industrial Research grant no 37(1693)/17/EMR-II, Department of Science and Technology as Ramanujan fellowship grant no. SB/S2/RJN-132/20/5. We are thankful to the Council of Scientific & Industrial Research (CSIR) and Ministry of Human Resource for a fellowship to Annu Rani and Shweta Jakhmola in the form of a research stipend. The funding organization has not played any role in the study design or the preparation of the manuscript. We appreciate our lab colleagues for their insightful discussions and advice. We gratefully acknowledge the Indian Institute of Technology Indore for providing facilities and support.

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