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Review

Archaic connectivity between the sulfated heparan sulfate and the herpesviruses – An evolutionary potential for cross-species interactions

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ABSTRACT

The structural diversity of metazoic heparan sulfate (HS) composed of unique sulfated domains is remarkably preserved among various vertebrates and invertebrate species. Interestingly the sulfated moieties of HS have been known as the key determinants generating extraordinary ligand binding sites in the HS chain to regulate multiple biological functions and homeostasis. One such ligand for 3-O sulfation in the HS chain is a glycoprotein D (gD) from an ancient herpesvirus, herpes simplex virus (HSV). This interaction between gD and 3-O sulfated HS leads to virus-cell fusion to promote HSV entry. It is quite astonishing that HSV-1, which infects two-thirds of the world population, is also capable of causing severe diseases in primates and non-primates including primitive zebrafish. Supporting evidence that HSV may cross the species barrier comes from the fact that an enzymatic modification in HS encoded by 3-O sulfotransferase-3 (3-OST-3) from a vertebrate zoonotic species enhances HSV-1 infectivity. The latter phenomenon suggests the possible role of sulfated-HS as an entry receptor during reverse zoonosis, especially during an event when humans encounter domesticated animals in proximity. In this mini-review, we explore the possibility that structural diversity in HS may have played a substantial role in species-specific adaptability for herpesviruses in general including their potential role in promoting cross-species transmission.

Contents

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1. Introduction

When the evolutionary time scale of herpes simplex virus type-1 (HSV-1) or type-2 (HSV-2) origin is reviewed, the evidence suggests that these simplex viruses arose via host-virus codivergence and cross-species transmission [1]. In fact, a recent report discovered novel HSV from wild gorillas, bonobos, and chimpanzees by screening fecal samples [1]. One astonishing finding of this report is that phylogenetic data analysis indicated that the simplex viruses from these African apes are all more closely related to HSV-2 than to HSV-1 resulting in HSV-2 as one of the earliest zoonotic pathogens [1]. It is believed that the simplex viruses infecting African great apes subsequently experienced multiple cross-species transmission [1]. Since primates are naturally infected with many types of herpesviruses [2,3], the above findings redraw our attention regarding the archeovirology of human herpes simplex viruses and their stable association with nonhuman primates for millions of years. However, the importance of heparan sulfate (HS) as the commonality that allows for herpesviruses to co-evolve and infect a variety of species has recently become paramount to our understanding of this process.

HS performs many functions in the animal host, in addition to serving as a receptor for many viruses [4–7]. The variable polysaccharide chains of HS covalently attached to a protein core in the form of heparan sulfate proteoglycans (HSPG) play a vital role during embryonic development and regulatory processes to maintain cellular homeostasis [8,9]. In this regard, it is not surprising that HSPGs are equipped with multi-tasking abilities because they interact directly and/or indirectly with large numbers of protein molecules. The basis of such interactions is because the chains of HS are highly diverse. The molecular diversity in HS stems from the series of modifications during its biosynthesis in which multiple enzymes generate unique sulfated moieties for multiple protein ligands including viral envelop proteins [10–15]. The biosynthesis of HS is a highly controlled sequential process that is initiated in the ribosome followed by translocation to the endoplasmic reticulum and Golgi, where the assembly of the tetrasaccharide linker region on serine residues of the protein core are initiated [8]. In the subsequent steps, polymerization proceeds by the addition of alternating uronic acid [D-glucuronic acid (GlcA) or L-iduronic acid (IdoA)] and D-glucosamine (GlcN) disaccharide units followed by a series of modifications. The HS-modifying enzymes include glycosyltransferases, epimerase, and sulfotransferases, which sequentially and progressively modify the HS stem. For instance, during the first step, N-deacetylation, and N-sulfation of N-acetylglucosamine (GlcNAc) occurs, converting it to N-sulfo-glucosamine (GlcNS). Next is the C5 epimerization of GlcA to IdoA followed by O-sulfation, which is performed by 2-O-sulfotransferases (2-OSTs), 6-OST, or 3-OST in the following order: Initially, 2-O-sulfation of IdoA and GlcA occurs followed by 6-O-sulfation of GlcNAc and GlcNS units and, finally, 3-O-sulfation of GlcN residues [4,8]. Matured HSPG localizes either to the membrane or the extracellular space providing unique and distinct binding sites for various proteins, which in turn provide functional specificity in a given biological process occurring in the host. Over the millennia, the level of sulfation of HS has decreased. While the level of sulfation is high in numerous aquatic species, evolution has promoted the conservation of a more limited number of modified HS forms in more advanced organisms (Fig. 1 A). In the future, it will be interesting to test if the rare modification in HS like 3-O sulfated HS may have impacted viral preference for specific hosts and host tissues. Concurrently, the modifications of HS residues also provide unique opportunities for various pathogens to interact with the host cell during cell entry [10,16–22]. Since viral zoonotic infections are on the rise [23,24] (Table 1), understanding shared receptor usage between the natural host and the zoonotic host, especially in the context of HS and its modified form(s) may provide clues to better understand the pathogenesis of these viruses, and their potential role in the zoonotic transmission [25–27].

2. Herpesviruses and heparan sulfate – a potential link for cross-species interaction and zoonotic evolution

The order Herpesvirales consists of a large number of animal viruses that have large, double-stranded DNA genomes and share a defining virion structure. In general, herpesviruses have been discovered in vertebrates from fish, reptiles, non-human primates to humans, and in some invertebrates (bivalves and gastropods) [28]. In addition to the characteristics listed above, another commonality of almost all herpesviruses studied is the importance of HS or modified HS in their entry process. The structural heterogeneity in the HS chain generates unique binding sites for multiple ligands making HS one of the most valuable biological molecules of life [8,9]. The most classic documented virus to exploit this to its fullest is HSV-1 which uses HS for cell binding followed by 3-OS HS to mediate virus-cell fusion even in the absence of any other protein receptor [5–7,10]. Piret et al., 2000 further demonstrated the importance of HS in HSV infection of murine and monkey cells when they identified that an inhibitor of sulfated polysaccharides, including dextran sulfate, prevented the binding of HSV to cell surface HS receptors and their entry into cells in murine and monkey cells [29]. Another zoonotic herpesvirus, Ostreid Herpesvirus 1 (OsHV-1), which targets bivalved and Pacific oysters, [30] is also inhibited from infecting their target organism when they are treated with the negatively charged sulfated polysaccharide dextran sulfate [30]. Future studies undertaking structure-function analysis for universally conserved herpesvirus glycoproteins (gD; gB), which interact with HS and sulfated HS, are likely to provide critical information related to viral entry. For example, it will be important to understand if subtle changes in the viral epitopes during the evolutionary process have given viruses a unique opportunity to use additional receptors in combination with HS and sulfated-HS receptors to advance cell infectivity. Taken together these findings implicate the conserved usage of HS for herpesvirus entry from invertebrates to vertebrates.

HS can be modified by enzymes to create a HS stalk that contains numerous sulfate sidechains with multiple types of linkages. As mentioned above, the HS enzyme that adds the sulfate group determines the type of sulfation that occurs to HS. It has been shown that the specific sulfation of HS is critical for not only determining virus specificity, but also for the virus's zoonotic potential. For example, one member of the α-herpesvirus subfamily is herpes B virus (Cercopithecine herpesvirus 1; CeHV-1, Cercopithecine herpesvirus 2; CeHV-2) which are primate herpesviruses that infect rhesus macaques and have strong genetic, virological, and immunological relatedness to HSV of humans [31,32]. These viruses naturally infect macaques, and if transmitted to humans via the saliva of animal bites, scratches, or percutaneous inoculation, the exposed humans may develop an acute ascending encephalomyelitis with a mortality rate of ~80 % in untreated cases [33–35]. Since both humans and macaques are known to express HS together with the HS-modifying 3-OST-2 and 3-OST-4 isoforms, it is unknown if CeHV-1/2 infection in humans or macaques is dependent on the enzymatic modifications by the above 3-OST isoforms. Furthermore, the ability of the

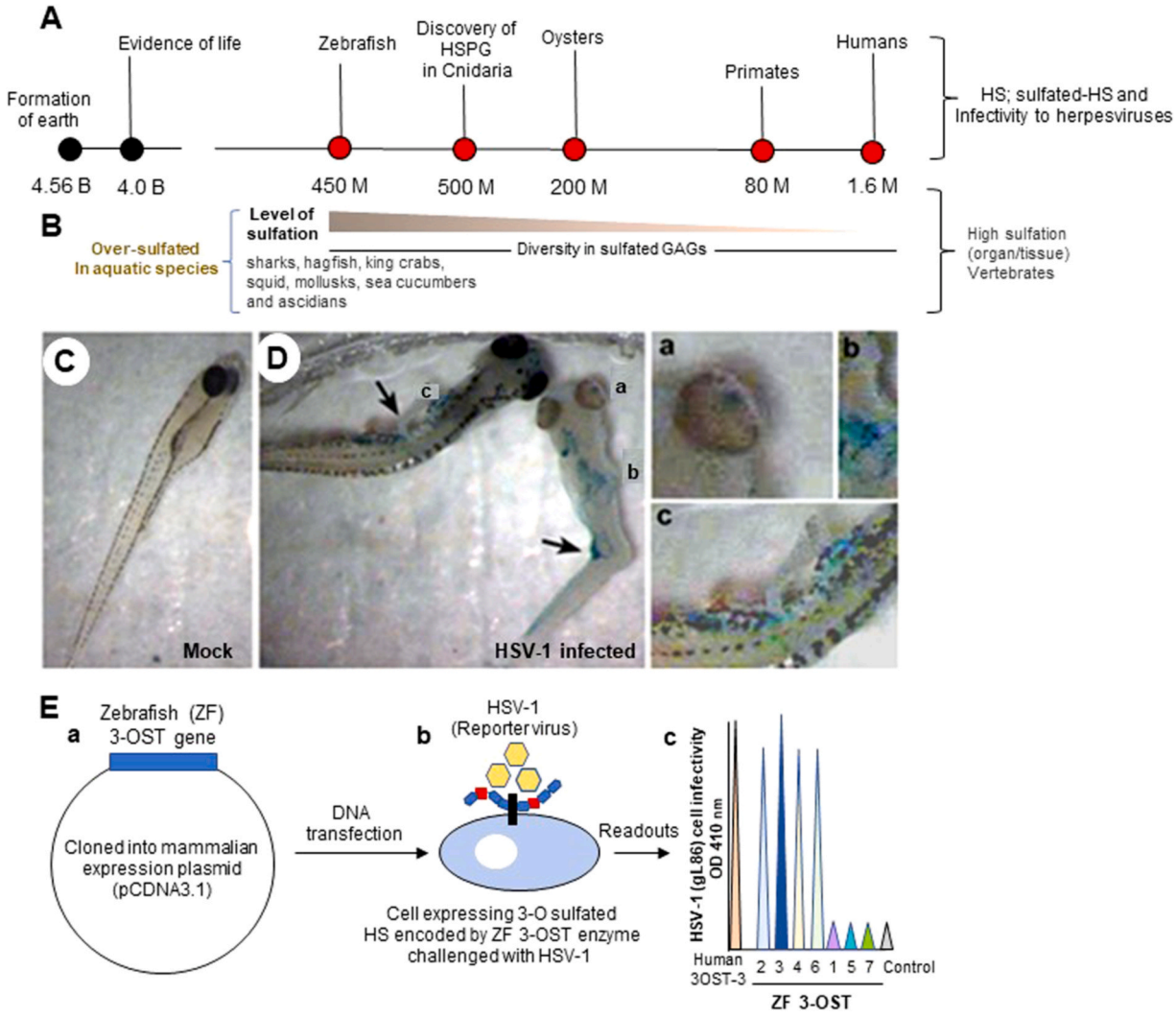

Fig. 1. (A). Schematic presentation tracking the timeline with the discovery of heparan sulfate proteoglycan (HSPG) in Cnidaria and the key targeted organism where herpesviruses have been shown to infect the organisms naturally or experimentally. (B). The known structural diversity in GAGs is being compared between primitive aquatic species and terrestrial vertebrates including humans. (C-D). A zebrafish embryo was either mock-infected (panel B) or infected with a reporter beta-galactosidase expressing HSV-1 gL86 (10^8 PFU) for 12 h and stained with x-gal (panel C). The regions in the infected embryos are further highlighted in panels a (eye), b (brain), and c (crooked urogenital tract area; also shown in the arrows). (E). Cloning of individual zebrafish encoded 3-O-sulfotransferase (3-OST) isoforms were carried out using mammalian expression plasmid (panel a), followed by transfection into CHO-K1 cells which are resistant to HSV-1 entry (panel b). Upon infection with the reporter HSV-1, zebrafish 3-OST-2, 3, 4, and 6 isoforms supported the viral entry compared to heparan sulfate alone (control), while 3-OST-1, 5, and 7 did not affect HSV-1 entry.

Table 1
Herpes viruses infecting animals and humans with the potential for zoonosis and reverse zoonosis.

Animal herpesviruses /subfamily	Host	Zoonotic potential
Feline herpesvirus type 1; *Alphaherpesvirinae*	Cat	Not known
Canine herpes virus-1; *Alphaherpesvirinae*	Dog	Not known
Cercopithecine herpesvirus 1; *Alphaherpesvirinae*	Macaque monkeys	Yes [31,32]
Cercopithecine herpesvirus 2; *Alphaherpesvirinae*	Macaque monkeys	Yes [31,32]
Pseudorabies virus; *Alphaherpesvirinae*	Swine	Secondary host [97–99]
Marek's disease virus; *Alphaherpesvirus*	Poultry (Chicken)	Yes [41]
Equid Herpesvirus 1; *Alphaherpesvirus*	Equine	Secondary host [42]
Gallid herpesvirus 2; *Alphaherpesvirinae*	Birds	Secondary host [43]
Phocid herpesvirus 2; *Gammaherpesvirinae*	Seals	*In vitro* [100,101]
Elephant Endotheliotropic Herpesvirus; *betaherpesvirus*	Elephants	Not known
Saimiriine herpesvirus-2; *Gammaherpesvirinae*	Squirrel monkey	Yes [102]
Ovine herpesvirus 2; *Gammaherpesvirinae*	Cattle, swine	Not known
Alcelaphine herpesvirus-1; *Gammaherpesvirinae*	Wildebeest	Not known
Human herpesviruses/subfamily	**Host**	**Anthropozoonotic potential**
Human herpesvirus-1 (HHV-1); *Alphaherpesvirinae*	human	*Callithrix jacchus* [72]
Human herpesvirus-1 (HHV-1); *Alphaherpesvirinae*	human	*Aotus trivirgatus* [73]
Human herpesvirus-1 (HHV-1); *Alphaherpesvirinae*	human	*Hylobates lar* [74]
Human herpesvirus-4 (HHV-4); *Gammaherpesvirinae*	human	Dogs, canine cell line [103,104]

Herpesviruses known to interact with HS.

herpes B virus to enter the cells of its human host via a combination of receptors distinct from those for HSV-1 or HSV-2 [36] suggests a possible mechanism of enhanced neuropathogenicity associated with zoonotic infections [37,38]. This possibility seems likely since the direct role of sulfated moieties in the HS chain affecting neuropathology is also documented [39,40]. However, it remains a mystery if the variability in the sulfation patterns in HS among various zoonotic species may act as the driving force in the evolution of highly virulent strains with enhanced neurovirulence in vivo and is worthy of further inquiry.

Another herpesvirus that has zoonotic potential and also uses HS receptor for cell entry is Gallid herpesvirus 2 (GaHV-2), an avian alpha herpesvirus that infects chickens and therefore is a major concern in the poultry industry [41]. The evidence that GaHV-2 relies on cell surface HS for viral entry stems from the fact that heparin inhibits plaque formation, and the pretreatment of susceptible chicken embryo fibroblasts with heparinase reduces the GaHV-2 infectivity [42]. Studies have also found GaHV-2 herpesvirus DNA in human serum [43] and an association between human carriage of GaHV-2 and the development of multiple sclerosis [44]. These data indicate not only a zoonotic transmission between chickens and humans but implies a common HS moiety that may allow for zoonotic infection between the two species.

3. Heparan sulfate – ancient molecule exploited by HSV-1 from primitive zebrafish model to humans

As mentioned above, it is fascinating that phylogenetic analysis reveals that HSPG originated around 500 million years ago when its presence was reported in a metazoan organism, Cnidaria [3] (Fig. 1 A). In addition, the unique patterns and the contents in HS sulfation (over sulfation to moderate sulfation) are different from aquatic species to terrestrial species (Fig. 1B). Interestingly, species-specific herpesviruses have also been shown to infect a wide variety of ancient organisms such as oysters, zebrafish, birds, reptiles, amphibians, and primates [45–49]. Since the receptor usage is known to be a key determinant for virus infectivity along with their involvement in disease development [50,51], it is logical to ask if sulfated HS may have played a role during viral entry in the primitive and advanced forms of life infected with herpesviruses.

Since zebrafish express an array of HS-modifying enzymes [52], our group was the first to recognize that embryonic zebrafish could be used as an experimental model to study HSV-1 entry and anterograde and retrograde trafficking. We found that this model includes multiple key pathological findings associated with the virus either in the brain or in the eye [53–59]. For example, a two-day-old zebrafish embryo challenged with a beta galactosidase-based reporter human HSV-1 not only shows virus infectivity, but also demonstrates several clinical features which are associated with human HSV infection (Fig. 1C-D). A pronounced x-gal staining in the HSV-1 infected zebrafish embryos was noticed, especially in the regions of the eyes and in the brain, mimicking human clinical pathology. Interestingly, the presence of HSV-1 also resulted in a developmental impairment in the zebrafish as the developing embryos visually looked crooked in appearance compared to mock-infected embryos suggesting the teratogenic potential of HSV-1 (Fig. 1C-D). The finding that zebrafish show a specific morphological defect may prove informative about the mechanisms and prevention of HSV-teratology [60]. As these effects were detected as scoliosis of the spinal cord, and in the eye, brain, and genital areas quite early in development, it is hypothesized that HSV, or the resulting physiological effects, interact with identifiable morphogenic processes. One prominent candidate process is the retinoic acid pathway (Vitamin A pathway) which supports the axial development of vertebrate embryos and key developmental events such as the closure of the neural tube [61]. While heavily studied for its role in development, retinoid signaling is also heavily involved in immune system function [62], including the induction of recognition receptors [63,64]. Prior research indicates that among adult rats, retinoid deficiency leads to hypersensitivity to HSV infection, with earlier onset of serious symptoms and increased severity of inflammatory and immune responses [65,66]. There are also indications that retinol supplementation shows promise as a preventative and therapeutic treatment for infection [67,68]. To our knowledge, it is unknown whether the presence of HSV interferes with typical retinoid receptor expression or the relative presence of their ligands; however, it is hypothesized that if HSV causes the up- or downregulation of retinoid receptors as other pathogens do [69], it may have serious consequences on development. Future research may be necessary to test the relevance of such mechanisms to HSV teratology.

As mentioned above, zebrafish are known to express diverse members of HS-modifying enzymes, including HS-modifying 3-OST enzymes [52]. Therefore, it was logical to test the impact of zebrafish-encoded 3-OSTs isoforms in HSV-1 entry. A mammalian expression cloning approach with zebrafish and human encoded 3-OST-3 gene transiently transfected individually into HSV entry-resistant Chinese hamster ovary (CHO-K1) cell was utilized [57] (Fig. 1E). We noticed that in entry-resistant CHO-K1 cells, the HS moieties generated by zebrafish 3-OST-2, −3, −4, and −6 isoforms, but not plain type HS, resulted in rendering CHO-K1 cells susceptible to HSV-1 entry. In contrast, the expression of zebrafish encoded 3-OST-1, −5, and −7 did not contribute to HSV infection, suggesting preferential domains in sulfated HS are utilized by the HSV-1 during cell entry into zebrafish [57]. Upon further inspection, we found that a group of 3-OST gene family isoforms especially 3-OST-2, −3,- 4, and −6 had conserved catalytic and substrate binding residues required for entry mediating activity of the enzymes, while the other group (3-OST-1, −5, and −7) lacks these properties [57]. In addition, the positive effect of zebrafish-encoded 3-OSTs in viral entry was also consistent with syncytia formation further suggesting the potential role of 3-OST in virus cell-to-cell spread [57]. The in vivo zebrafish model is a useful tool to understand HSV-1 infection and the requirements of HSV-1 for its potential cross-species zoonotic infections [52]. In addition, due to the abundance of HS, especially the sulfated domains in HS in primitive aquatic organisms like zebrafish, it can be reasonably argued that the infectious agents targeting aquatic life, including species-specific herpesviruses, might have played a significant role in the evolution of diversity in HS [70]. Similarly, it is possible that viruses being intracellular pathogens during co-evolution, selected certain sugar-mimicking regions on their envelope in the form of host-derived glycans to escape the host immune response while maintaining their identity [71]. It remains unclear if such glycans also generated higher affinity for viral entry receptors during virus-host cell interactions. Understanding this complex yet successful relationship between the pathogen and the host could provide a clue for successful intervention in the future.

4. Heparan sulfate & reverse zoonosis

In contrast to the potential zoonotic threat from some of the herpesviruses, the reverse, which is the infections to the animals from the human herpesviruses is also documented in the literature (Table 1). For instance, an outbreak of classical herpetic vesicoulcerative stomatitis in a family group of marmosets (*Callithrix jacchus*) has been reported where HSV-1 was identified as the causative agent [72]. Similarly, HSV-1 infection in new world primates with a fatal disease is also well documented [73,74]. Interestingly, Old World primates appear to be less susceptible to HSV-1 and infection mimics in terms of clinical signs than those of humans [75–77]. However, the interaction of the human population, in general, is low with marmosets and Old-World primates. Therefore,

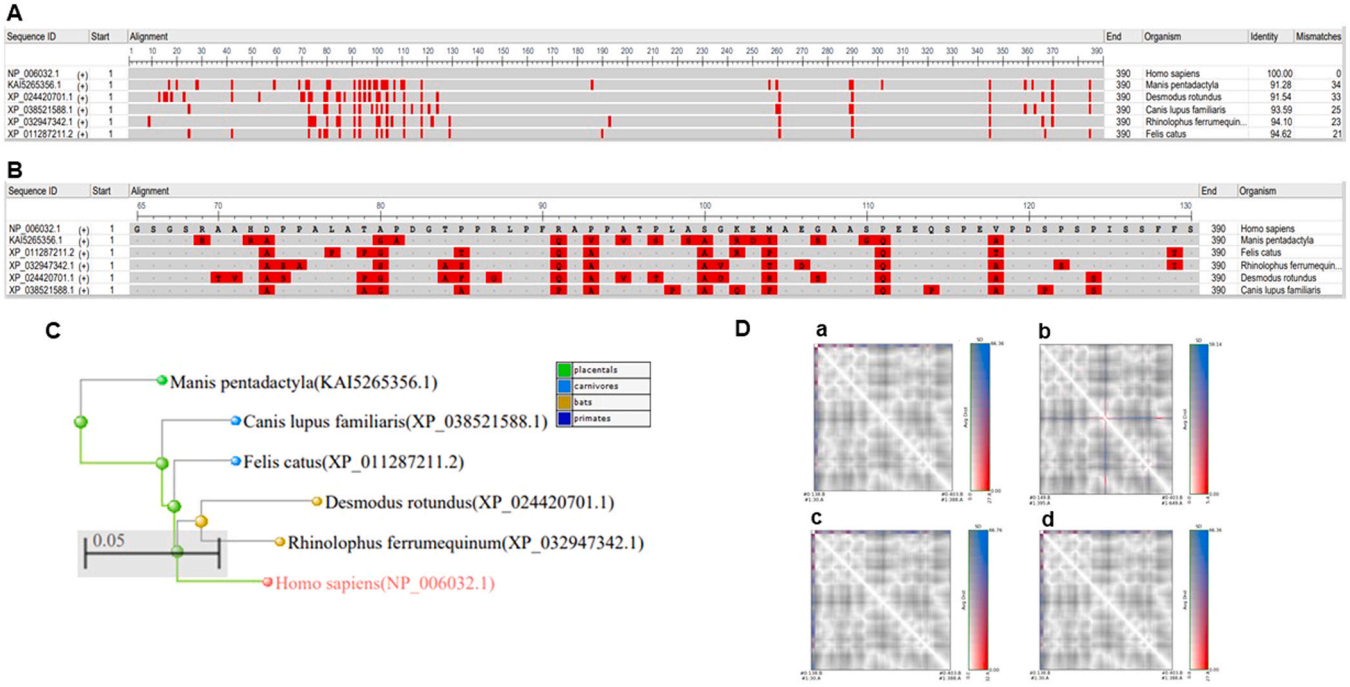

Fig. 2. Multiple sequence alignment of Human 3-OST-3 protein with homologous protein from various animal species using COBALT tool (https://www.ncbi.nlm.nih.gov/tools/cobalt/cobalt.cgi) which finds a collection of pairwise constraints derived from conserved domain database, protein motif database, and sequence similarity, using RPS-BLAST, BLASTP, and PHI-BLAST. (A). Frequency-based differences within the full sequence of 390 amino acids. Darker shades of red indicate a further difference from residues in other rows in the alignment at that position. (B). Residues that occur infrequently in the region from 65 to 130 aa region are zoomed to show particular amino acid mismatches between the sequences. (C). Phylogenetic tree based upon multiple sequence alignments of 3-OST-3 protein from different species showing the evolutionary relationships between homologous sequences. The scale bar represents a phylogenetic distance of 0.05 nucleotide substitutions per site measured on the graph. (D). Residue-residue (R-R) distance map along with their standard deviation (SD) for 3-OST-3B enzymes expressed by cat (panel a), dog (panel b), horseshoe-Bat (panel C), and humans (panel d) are analyzed. The residue distance for each species was measured and correlated to the 1t8U. The vertical bar indicates the average distances and the horizontal number indicates their SD of the respective distance. Residue-residue distance for the proteins was computed using RRDistMaps in UCSF Chimera. The distance map generates the protein contact map where the pair of residues are marked as contacting or non-contacting based on the distance cutoff criterion. Here, the Cα-Cα between the protein chains are shown along with their average distances and their standard deviations.

we sought to ask whether domesticated animals and other potential zoonotic sources expressed 3-OST enzymes that are similar to human 3-OST, which would potentially make these cells susceptible to HSV-1 infection. As shown in Fig. 2, we performed multiple sequence alignment (Fig. 2A-C) and residue-residue (R-R) distance mapping (Fig. 2D) of human 3-OST-3 protein with homologous protein from various animal species such as domesticated dogs and cats, as well as recently described potential sources of zoonotic transmission: pangolins and bats. As shown in Fig. 2A-C, the canine- and feline-encoded 3-OST-3 isoforms are 91 % and 89 % homologous to human 3-OST-3 isoforms. Bat and pangolin 3-OST-3B enzymes were 91–94 % similar to human 3-OST, despite mismatch residues observed between 65 and 130 aa residues. R-R distance mapping data also suggests that 3-OST-3B genes show similar patterns in terms of protein contact with modest variability observed in canine-encoded 3-OST-3B compared with human, feline, and bat 3-OST-3B isoforms (Fig. 2D). Due to this high level of sequence homology, we cloned the 3-OST-3B gene into mammalian expression plasmids and transfected these plasmids into HSV-1 resistant CHO-K1 cells (Fig. 3A). After transfection, the cells were exposed to HSV-1 that carried a reporter beta-galactosidase enzyme, and looked for the presence of β-galactosidase positive cells. As shown in Fig. 3A-B, HSV-1 resistant CHO-K1 cells transiently transfected with individual zoonotic species (dog, cat, bat, pangolin) encoded 3-OST-3B isoforms were susceptible to HSV-1 infection, suggesting the potential of 3-OS HS in cross-species interactions. In Fig. 3B, a reporter HSV-1 virus was used to quantify relative viral entry from each zoonotic species 3-OST-3B isoform. The viral entry values for each species' 3-OST-3B isoform were then divided by the viral entry values for Human 3-OST-3B and percentages were generated. The resulting figure represents the relative success of each zoonotic species 3-OST-3B isoform as an HSV-1 entry receptor compared to Human 3-OST-3B. The above quantitative data of HSV-1 entry was also complemented by using an x-gal assay which also showed that all species 3-OST-HS were capable of converting HSV-resistant CHO-K1 into susceptible cells (Fig. 3C). Based on these data, it is clear that human herpes simplex virus-1 can recognize the 3-O modifications generated by various zoonotic species. Additionally, we were able to demonstrate that the viruses generated from cells expressing different zoonotic 3-OST enzymes were able to induce plaque formation as an indication of cell-to-cell spread (Fig. 4). Although herpesviruses are highly species-specific, these data suggest that they pose a zoonotic or reverse zoonotic threat (Fig. 3D). Future studies utilizing canine or feline herpesviruses against human 3-OST-3B cells will be interesting to investigate if the above animal herpesviruses show a higher affinity for human receptors to promote viral entry. Ultimately, based on these data, the close contact between humans and animals may result in cross-species transmission and needs to be closely monitored.

5. Heparan sulfate as a translational target for zoonotic herpesvirus infections

Based on the data above, Herpesviruses have significant potential for zoonotic transmission, and in some cases, with devastating results for humans [33–35]. Therefore, the identification of evolutionarily conserved drug targets may be beneficial for the treatment of zoonotic diseases. Given the structural diversity of HS across many species, it seems critical to map the regions which interfere with the virus infectivity, including the detrimental outcome in the form of

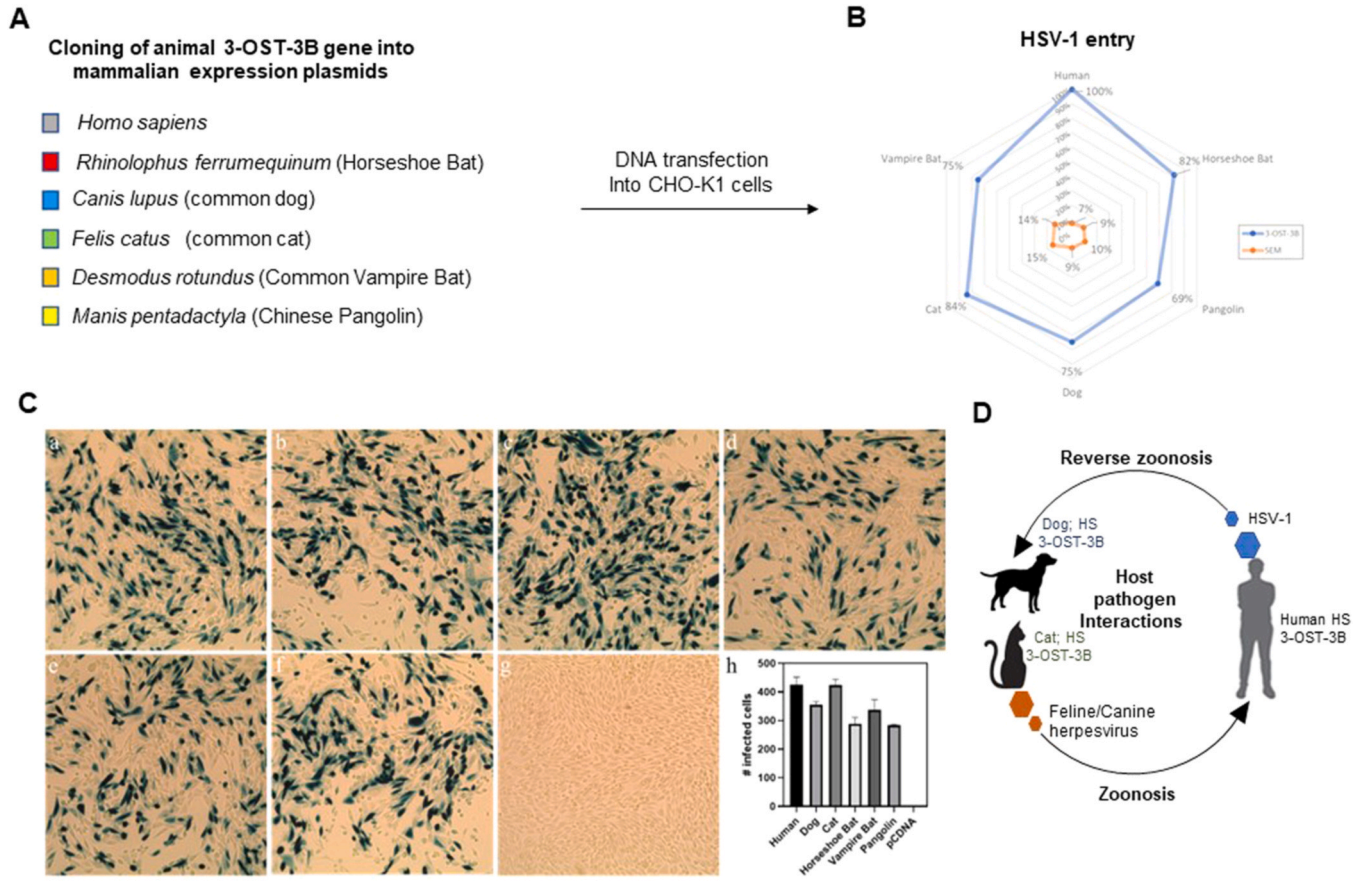

Fig. 3. Enzymatic expression of 3-OST-3B from various animal species renders CHO-K1 cells susceptible to HSV-1 entry. (A, B) Cloning of the 3-OST-3B gene from various animal species into mammalian expression plasmid pCDNA3.1 followed by DNA transfection of individual 3-OST-3B into resistant CHO-K1 results susceptible to HSV-1 entry. (C). HSV-1 entry in CHO-K1 cell expressing individual 3-OST-3B was quantified by using reporter beta-galactosidase assay. (D). CHO-K1 cells expressing individual 3-OST-3B ranging from human (a), horseshoe bat (b), dog (c), cat (d), vampire bat (e), pangolin (f), empty vector (g) challenged with HSV-1 to visually estimate and quantify the number of blue cells (a-h) as an indicator for viral entry using X-gal assay. (E). Proof of concept that human herpes simplex virus can potentially infect cells expressing either dog or cat-encoded 3-OST-3B. However future studies are needed to test if feline herpesviruses can potentially infect cells expressing human 3-OST-3B gene.

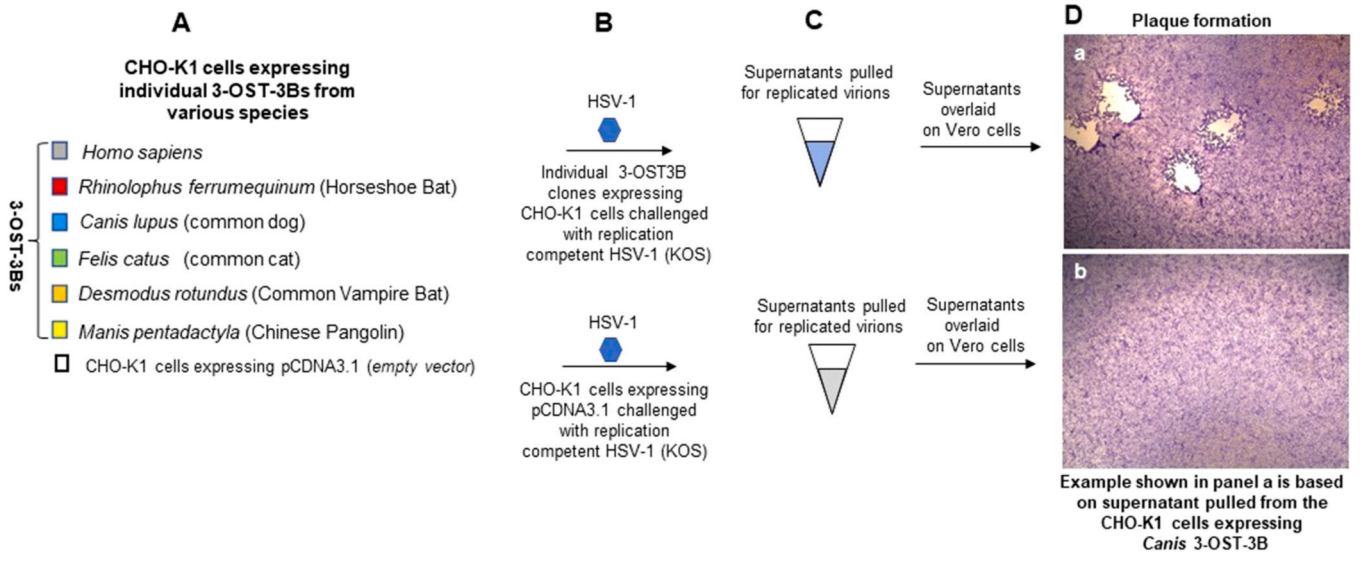

Fig. 4. Significance of 3-OST-3B modified heparan sulfate in mediating HSV-1 cell-to-cell spread. CHO-K1 cells expressing individual forms of the 3-OST-3B gene from various sources (A) and challenged with replication-competent HSV-1 (KOS-84) (B), followed by supernatant collection (C) to challenge Vero cells (D). Shown in panel D, is the supernatant pulled from the CHO-K1 cells expressing an empty vector (a) and the Canis 3-OST-3B (b) and laid onto Vero cells.

inflammation and the severity of disease. Our previous study laid the proof of concept by mapping unique domains in HS and 3-OS HS using phage display technology [16]. This approach generated a unique library of potential binders of which two anti-HS and anti-3-OS HS peptides displayed strong antiviral activities against multiple herpesviruses. These peptides represent an attractive antiviral to be

Table 2
Significance of cell surface heparan sulfate in cell infectivity in reference to zoonotic viruses.

Zoonotic viruses	Significance of heparan sulfate
Zika virus	Glycoprotein E interacts with HS; virus entry/replication [105]
Dengue virus	Secreted NS-1 interacts with HS; virus cell binding [106]
Chikungunya virus	Glycoprotein E2 interacts with HS; N-sulfation; virus cell binding [107]
Rift Valley Fever Virus	Co-receptor; virus entry [108]
Japanese Encephalitis virus	Highly sulfated form of GAGs; virus entry [109]
Ebola virus	virus entry in polarized epithelial cells; Exotosin 1 [110,111]
Marburg virus	Exostosin 1 (EXT1); virus entry [111]
Nipah virus	Co-receptor; virus entry [112]
Human immunodeficiency virus	gp120 and p17 interactions with HS; virus entry [113]
SARS-CoV-2	Co-receptor; virus entry [114]
Hantavirus	Co-receptor; virus entry [115]
Rabies virus	N sulfation and 6-O-sulfation; virus entry [116]
Influenza A virus	HS sulfation; modulation in severity of disease [117]

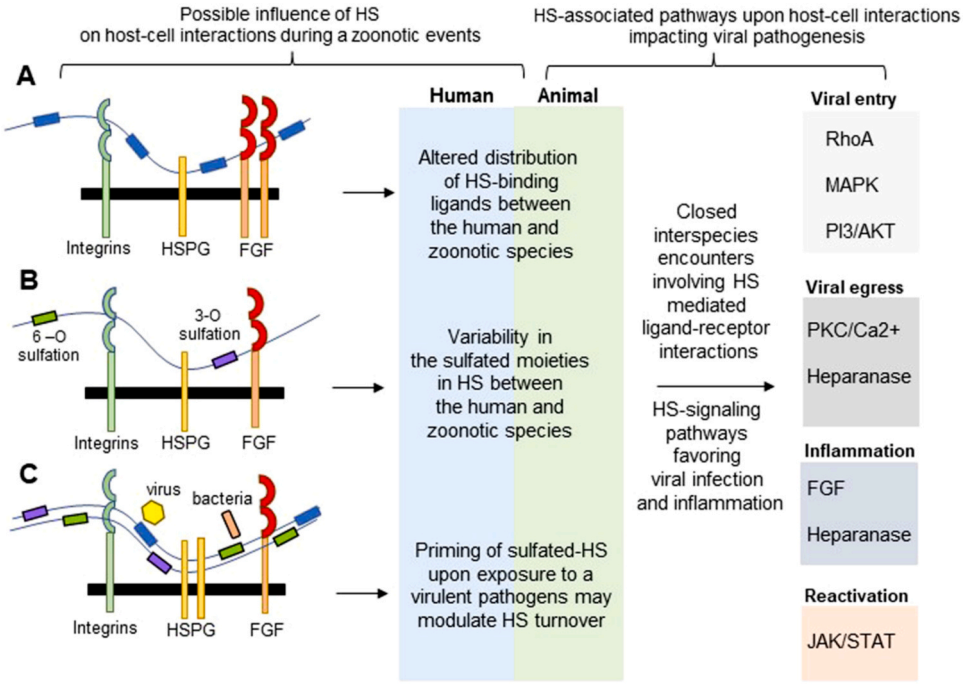

Fig. 5. Possible involvement of heparan sulfate during virus-host interactions. (A). HS functions by tethering to HS-binding ligands, and therefore loss or gain of HS in the ligand-expressing cells and tissues could result in altered distribution of these ligands which may impact virus infection. (B). Similarly, variability in the distribution of sulfated HS between human and zoonotic species further may influence virus cell and tissue tropism in a given species. (C). Finally, the priming of sulfated-HS among various zoonotic species upon regular exposure to a new pathogen may modulate HS turnovers thereby affecting the virus pathogenesis. (D) HS-dependent signaling promoting viral entry/spread is highlighted.

screened against viruses of zoonotic origin given the fact that zoonotic diseases are on the rise. Similarly, it should be possible to design and screen small HS mimetics and heparanase inhibitors that specifically disrupt various stages of virus-cell interaction including HS-chemokine interactions in context to prevent viral zoonotic diseases [22].

Finally, an additional member involved in the process of viral infectivity is cellular heparinase – an endoglycosidase with the unique ability to degrade HS. This enzyme is also an evolutionarily conserved glycosaminoglycan present ubiquitously at the cell surface and extracellular matrix (ECM) in various cell types. Many viruses, including HSV-1 are known to upregulate heparanase activities thereby clearing the HS from the cell surface, which paves the way for the virus release and spread [78]. Therefore, a universal drug that blocks heparanase may represent a novel treatment intervention for long-term inflammation associated with HSV-1 infection as well as other zoonotic herpesvirus infections.

6. HSV effects on reproduction and across generations

Virus-host interactions evolve alongside the evolution of a host species, but lingering vulnerabilities can still be exploited by a virus and apply selective pressures to their host species. To the extent that they cause primary mortality, zoonotic diseases create selective pressures which promote the prevalence of restriction factors [79], processes that prevent pathogen effects from reaching lethal levels. Mendelian selection following highly lethal zoonotic infection has been documented on a rapid scale when species-specific viral agents have been used to manage invasive species, such as rabbits and cats [80]. However, a non-lethal infection can also be broadly impactful on a species to the extent that it influences fertility and offspring health/survival.

One frequently cited effect of HSV infection is male infertility, and while the rates of HSV have are not elevated among infertile men [81], direct evidence of impaired sperm characteristics has been

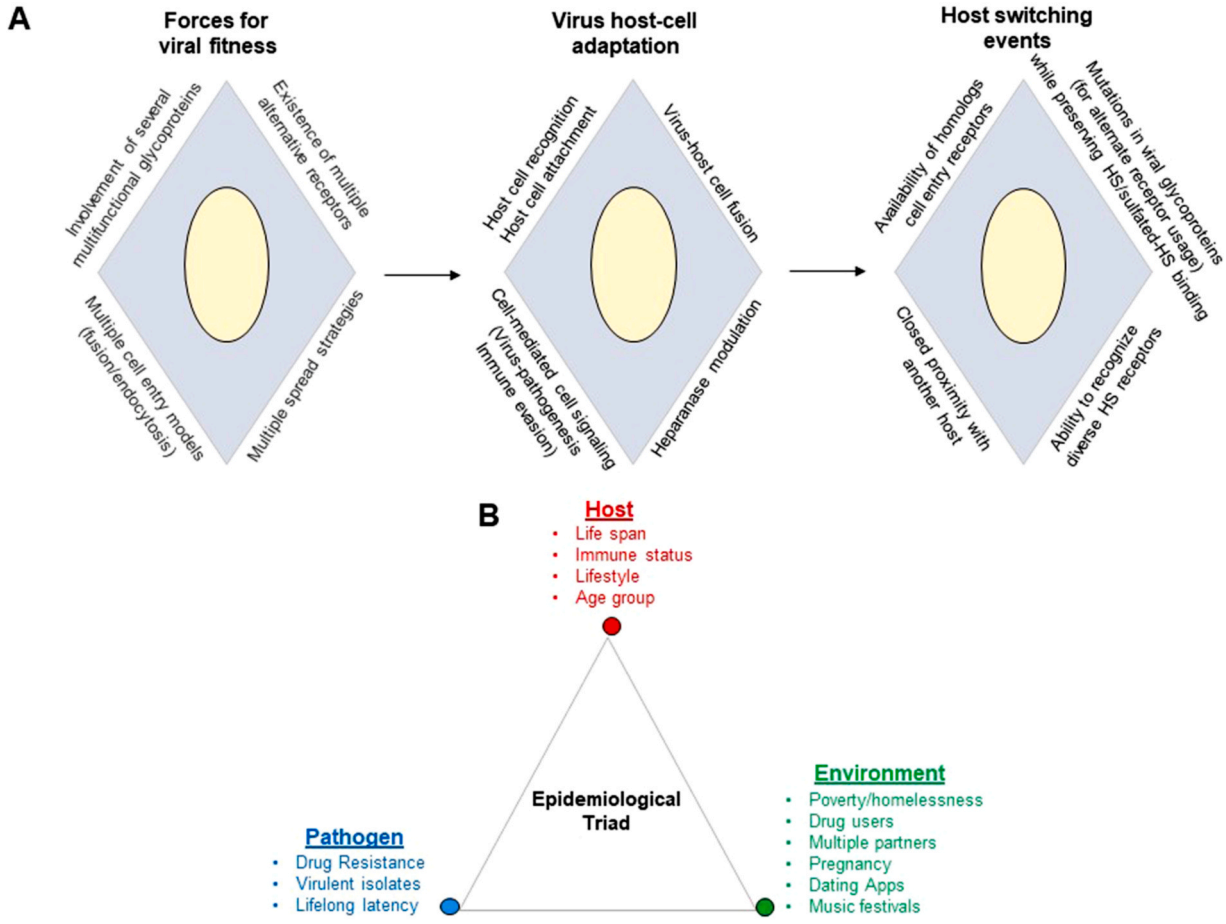

Fig. 6. (A). The role of cell surface heparan sulfate in viral fitness and host cell adaptation to influence directly or indirectly during a zoonotic event are highlighted. (B). A classical epidemiological triad under host-pathogen and environment highlighting the triggering factors for herpesvirus spread.

documented. For example, Kurscheidt et al., 2018 reported that among men seeking consultation for infertility, those with HSV-2 infection showed higher rates of hematospermia and lower seminal volume, while those with HSV-1 infection showed reduced sperm counts [82]. Other clinical studies provide varying evidence for the specific effects of HSV infection on sperm parameters and highlight that these effects may be exacerbated by common antiviral treatments [83–86]. Even so, the vulnerability of male reproductive organs or function and HSV infection has been documented in several mammalian species, including mice [87,88], horses [89], and dogs [90]. Where species appear to differ from one another is the manifestation of reproductive toxicity, with some mammalian species showing direct testicular damage, others show changes primarily in the health, quantity, or viability of sperm. Whether similar vulnerabilities are also present in non-mammalian species remains to be thoroughly studied; however, similar effects may be particularly impactful in species like fish, which require disproportionately large clutches of offspring to sustain a healthy adult population.

Human clinical literature also highlights the potential for HSV infection to contribute to complications during pregnancy and morbidity during early development. A meta-analysis indicated that HSV infection is associated with increased rates of miscarriage, stillbirth, and premature birth [91]. In successful pregnancies, infant mortality rates are similarly associated with infection [92]. HSV infection has also been shown to induce significant pathologies in the placenta including chronic placental inflammation, chronic chorioamnionitis and villitis, and necrotic conditions [93], which likely contribute to the associations between infection and pregnancy complications and/or failures.

In this review, we presented data indicating that in a non-mammalian model, zebrafish, embryonic infection with a reporter beat-galactosidase expressing HSV-1 produced severe morphological effects, indicating that the finding that early development is a particularly vulnerable period for infection is similarly present even in primitive vertebrate species. This is complemented by work with intermediate species like mice. For example, Patel and colleagues (2019) reported that exposure to either HSV-1 or HSV-2 was uniformly lethal in mouse pups within nine days or six days, respectively [94]. At non-lethal levels of infection, rodent offspring can show neurological dysfunction, including changes in locomotor output and increased anxiety-like responses [94,95]. Taken together, it is proposed that non-lethal health burdens associated with HSV infection, including infertility, impaired maternal health or offspring survival, and chronic diseases stemming from developmental infection, add to the selection pressure that zoonotic pathogens like HSV exert upon their host populations.

7. Summary

In this review we discussed the relationship between a 500-million-year-old HS and an ancient, well-documented herpesvirus. Although the detailed molecular mechanism by which herpesviruses may interact with zoonotic species or zoonotic agents that interact with human hosts via HS and 3-OS HS receptors has not been established, experimental evidence suggests that HS and 3-OS HS

receptors may play a significant role as evident from HSV-1 infection in the primitive zebrafish. Furthermore, the natural HSV-1 infections in the primates that encode HS-modifying 3-OST isoforms suggest that HS chains may have likely played a role in the early stages of virus evolution and host selection for herpesviruses. The in vitro-based studies have further demonstrated that HSV-1 glycoproteins can recognize and mediate virus entry and virus cell-to-cell spread using conserved 3-OST enzymes across a wide variety of zoonotic species (Fig. 3 and Fig. 4). This phenomenon raises many interesting possibilities that highly diversified sulfated domains in HS chain and their interactions with various pathogens were the initial driving force in the co-evolution of both HSPG in the host and unique HS recognizing epitopes on the virus envelope glycoproteins for natural selection. For instance, although the structural variability in HS is highly preserved over millions of years, the unique pattern and the contents in sulfation (over-sulfation to moderate sulfation) are different from aquatic species to terrestrial species (Fig. 1B) [70]. Certainly, infectious agents in general might have played a bigger role by exploiting the HS chain to evolve the host-pathogen relationship. Although it has been argued that over-sulfated HS regions were host protective against a variety of pathogens [70], in reality, Ostreid herpes viruses do infect oysters, clams, scallops, and other mollusks, which contain highly sulfated HS. One possibility also exists that the magnitude of the sulfation in HSPG evolved because of the mass/volume ratio of the species. Despite the changes made during the course of evolution in HSPG as a host protective mechanism, the viruses strategically may have developed unique epitopes to mask the change and yet utilize them for cell entry. The unique location of HSPG on the cell surface as well as on the glycocalyx may also have supported virus persistence in a given host [96]. Further, biochemical analysis that compares the affinity of zoonotic viruses for human HS and 3-OS HS along with epitope rendering may bring exciting new information. Since the host interactions with the entry receptor are important determinants concerning the outcome of the infection, novel therapeutics can be developed not only to treat fatal zoonotic infections but also equally dangerous anthroponotic infections. Since our current understanding of HS biosynthesis and the fine-tuning steps involved with the enzymatic modifications in HS are well established, we can utilize this knowledge to generate a target-based approach to prevent viral infection. This will require continuing collaborative efforts from multiple disciplines of biochemistry, structural biology, and infectious diseases. Given the significance of HS documented with zoonotic viruses (Table 2) during viral entry in general and the inflammatory cell damage, testing various 3-OST isoforms and the HS-mimetics directed against 3-O sulfated HS may also be useful to control viral spread. Due to the variety of roles HS plays including cellular signaling, we also predict that their distribution, priming, and the presence of available ligands may further modulate virus-host interactions (Fig. 5). Similarly, the ubiquitous presence of a molecularly diverse chain of HS together with the availability of multifunctional viral glycoproteins may aid in the viral fitness and host cell adaptation – a process which gives the virus a required sustainability during zoonotic events (Fig. 6). Although future studies will be needed to identify more precise regions in 3-O sulfated HS which may be involved in viral cell-to-cell spread among zoonotic species, for now, it is clear that HSV-1 offers a unique ability to recognize 3-O sulfated regions in HS from various species. Taken together, the spread of HSV infection to various other species could also be influenced by the type of sulfation, and HS turnover in a given host, which could also be a critical event in the evolution of the virus itself.

Author contributions

VT, MSM, DS contributed to conceptual design, acquiring funding. **VT, MSM, AH, AC, JE, V Tripathi** and **DJ** contributed to collecting and analyzing data, creating figures, and writing the manuscript. **CP** and **DMS** contributed for computational analysis.

Data availability

All data presented in this study are available on request from the corresponding authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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