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Rabies Virus Target Cell Specificity and Tropism

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Abstract:

Rabies virus (RABV), the causative agent of rabies, is an extremely neurotropic pathogen known to cause fatal encephalitis in humans and animals. The virus shows a high degree of cellular specificity for neurons and spreads efficiently along neural networks to access the central nervous system. It is important to elucidate the mechanisms that govern viral tropism, receptor interactions, and neuronal targeting. In this article, we provide a broad overview of the current literature on rabies virus target cell specificity and tropism. Illustration A total of published studies about viral structure, receptor-mediated entry, neuron- and non-neuron cell interactions, axon transport mechanisms and viral strain differences were reviewed to summarize current knowledge regarding host virus interactions and infection dynamics. The infection of the rabies virus is initiated by viral replication in peripheral tissues such as skeletal muscle cells followed by receptor-mediated entry into peripheral neurons at the neuromuscular junctions. The attachment and internalization of the virus are mediated by multiple host receptors, including nicotinic acetylcholine receptors (nAChRs), p75 neurotrophin receptor (NTR), neural cell adhesion molecule (NCAM) and metabotropic glutamate receptor (mGluR). Hosts Virus Glycoprotein Host Cell Entry Membrane Fusion Immune Evasion Upon entry, the virus hijacks dynein-mediated retrograde axonal transport to access the central nervous system in an immune privileged environment2. Additional data indicate that non-neuronal cells like astrocytes can also become infected by the virus and contribute to immune responses. Furthermore, vesicular stomatitis virus infection interferes with neuronal function by disrupting neurotransmitter signaling and axonal structure. Differences also emerge in neural circuit usage, as viral strain variance and host receptor distributions can shape the

viruses: host organism interface and drive differences in infection spread through neural circuits. Rabies virus is a neurotropic pathogen that causes fatal encephalitic disease in humans and mammals. This tropism for neural tissues and its spread through neuronal networks underpins the mechanisms of pathogenesis. This review discusses the host range and target cell requirements of rabies virus, with an emphasis on elucidating the molecular mechanisms that determine viral entry into cells, intracellular trafficking and host–virus interplay. The virus first replicates in peripheral tissues, mainly skeletal muscle cells, and subsequently spreads to peripheral neurons by receptor-mediated entry at neuromuscular junctions. Attachment and internalization of viral particles is facilitated by a number of neuronal receptors including nicotinic acetylcholine receptors, p75 neurotrophin receptors, neural cell adhesion molecules, and metabotropic glutamate receptors. The viral glycoprotein is involved in crucial processes like receptor binding, membrane fusion, and immune avoidance–all of which also directly influence the infectivity and pathogenicity of the virus. After entering, the rabies virus hijacks dynein-driven retrograde axonal transport to access the central nervous system while evading immune detection. Besides neurons, accumulating evidence indicates that non-neuronal cells including astrocytes may play a role in viral persistence and innate immune modulation. In addition, the infection causes considerable changes in neuronal function: disruptions to neurotransmitter signaling and axonal integrity. Specificity and efficiency of viral spread within neural circuits is additionally influenced by viral strain variation and host receptor distribution. Molecular determinants of rabies virus tropism need to be established, as they not only further our understanding of viral neuro-pathogenesis, but also pave the way for optimised human health therapeutic approaches and enhanced safety in synaptic tracing with rabies-based eukaryotic viruses. The tropism of rabies virus is determined by a complex interplay of viral structural proteins, host receptor availability, and neuronal transport processes. Collectively, these processes facilitate effective neuroinvasion and throughout the nervous system dispersal. These findings provide insights into the molecular and cellular processes underlying rabies viruses; such knowledge will support improv ed antiviral strategies, as well as vaccine design, or safer rabies-based viral tools for neural circuit mapping in neuroscience studies.

Keywords: Rabies virus (RABV); Neurotropism; Viral tropism; Receptor-mediated entry; Axonal transport; Neuronal infection, acetylcholine receptors (nAChRs),

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Introduction

Rabies virus is known for the severity of its neurotropism, as it penetrates the peripheral nervous system and replicates millions of times before retrograde axonal transport to reach the central nervous system [1]. Once inside the neuronal soma, the virus undergoes replication cycles that favor trans-synaptic spread, enabling to cross peripheral immune defenses and establish chronic infection in neural tissues [2, 3]. Although neurons are the principal reservoir of replication [3], more recent studies uncover non-neuronal viral tropism, especially astrocyte infection, as a key mediator of CNS innate immune regulation [4]. The virus can successfully evade glial surveillance by blocking the production of type I interferons, leading to replication and persistence within an immunologicaly quiescent neural milieu [5]. Moreover, such a non-canonical interaction with astrocytes indicates that the virus does not depend solely upon synaptic transmission but may exploit a wider spectrum of glial cell populations as vehicles for its spread [2]. Mathematical modelling of infection dynamics indicates that the variation in the expression levels of glycoproteins among different strains plays a key role in determining how efficiently this type of glial cell entry occurs [4].

In fact, transcriptomic profiling suggest that these viral-host interactions stimulate different pathways intracellularly emphasizing how differential genes expression in glial populations can restrict or facilitate the virus replication [6]. Outside of these glial interactions, the selective binding to receptors (like nicotinic acetylcholine receptor and p75 neurotrophin receptor) is one of the core determinants for the virus's ability to start infection in peripheral neurons [7]. Following the entry to dorsal root ganglia and motor neurons, long-range retrograde transport allows for neuroinvasion with the pathogen co-opting these pathways as means of transgressing peripheral architecture in the host [6]. The introduction describes the extraordinary neuroinvasiveness of rabies virus and its immune evasion with effective access to the central nervous system. What is also important is that there is clear evidence from this study, taken together with earlier findings on rabies virus indicating neuronal and non-neuron cells virus's replication including astrocytes as well implication in understanding more complex infection strategy than it was thought. Viral spread in the nervous system, therefore, seems not to be restricted merely to neuroanatomical routes based on neuronal synaptic circuits but instead likely includes glial-mediated pathways

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of virus spread as well. The neurotropism and receptor-mediated entry of the rabies virus into peripheral neurons are closely tied to its pathogenesis. However, new evidence indicates that glial cells also participate in viral persistence and immune evasion, thus broadening the identification of cellular rabies virus targets within the nervous system.

Rabies Virus Structure and Genome

This viral architecture is characterized by a bullet-shaped morphology surrounding an unsegmented, negative-strand RNA genome that acts as the template for transcription and replication in sequence. It is the glycoprotein (G) that mediates binding to specific host receptors present at the cell surface, as well as pH-dependent membrane fusion in endosomes, and thus serves as a key bottleneck for cellular tropism [8]. More the more recent studies show, this surface protein also uses its PDZ-binding motif towards interfering with neuronal enzyme regulation to modulate the host cell physiology in a way that will promote viral persistence [9]. Simultaneously, the matrix protein mediates assembly of viral ribonucleoprotein complexes by bridging them with the glycoprotein to produce infectious progeny [10]. Moreover, the viral phosphoprotein and polymerase complex drive transcription of these genes in the cytoplasm by tightly controlling the temporal expression pattern of all viral proteins to coordinate with the replication cycle while escaping host detection [11]. In addition, the variable incubation period seen in clinical cases is at least partially due to initial replication times required at peripheral inoculation sites where the virus may skip over the motor endplates if titers are low enough. These interactions, together with the virus's capacity to hijack cellular machinery, is mediated when specific polymerase proteins (like L polymerase) target host factors during viral genome synthesis in limited cytoplasmic conditions [12, 13].

Additionally, the interaction of the nucleoprotein with the host importin system highlights another layer of sub-cellular localization that promotes pathogenic survival through efficient nuclear trafficking [14]. With the genomic RNA assosciated with N, P and L proteins forming the stable ribonucleoprotein complex during its travel through a dense cytoplasmic milieu and thereby ensuring that the viral genome is protected from host nucleases [15]. The structural integrity of retroviral protein products is ensured thanks to the highly ordered helical nucleocapsid, acting as a stable scaffold for the

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orderly assembly of viral mRNAs and full-length antigenomic templates [16]. Studies comparing rabies and closely related rhabdoviruses have shown that the nucleoprotein retains harmonised structural folding topologies required to control the viral transcription-replication switch [17]. Additionally, the N-terminal and C-terminal domains of the nucleoprotein are essential interaction surfaces for host cellular factors that actively modulate L–P complex enzymatic activity at these divergent phases of synthesis [9, 18]. This structural organization of the nucleocapsid protects the delicate viral RNA from cytoplasmic degradation and showcases it in a fold recognized by the RNA-dependant RNA polymerase [19].

Rabies virus is highly encoded for efficient replication and immune evasion. Transcription, replication, and virion assembly activities are all separately regulated by the combined action of various viral proteins (e.g. glycoprotein, matrix protein, and polymerase complex) in a finely-tuned system. The ribonucleoprotein stability is vital for both defending viral RNA and facilitating genome replication. The rabies virus genome and structural proteins constitute an integrated system that improves viral replication efficiency and protects the viral genome from host defenses. Insights gleaned from these molecular interactions can inform antiviral drug development and vaccine design.

Entry Mechanisms and Receptor Interactions

The first step in internalization of virus is usually at the neuromuscular junction where it mediates attachment to nicotinic acetylcholine receptors on motor endplates that initiates infection of peripheral nervous system [20]. Afterwards, the virus interacts with p75 neurotrophin receptor and neural cell adhesion molecule to allow for fast internalization followed by subsequent axonal transport [21]. Outside of these classical pathways, the binding of the rabies virus glycoprotein to low-affinity nerve growth factor receptor highlights a more complex approach for cell-type selectivity that goes beyond canonical synaptic engagement [22]. Further modifications of this entry process are mediated by the pH-dependent fusion activity of viral glycoprotein within endosomal compartments, resulting in release of ribonucleoprotein complex into neuronal cytoplasm [14]. In addition to these interactions, several studies have shown that other surface molecules (e.g. metabotropic glutamate receptor subtype 2 and heparan sulphate) help widen viral tropism by providing alternative docking sites along

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with a variety of different neuronal and non-neuronal cells [23]. Additionally, structural analyses of the viral glycoprotein and mapping its interactivity with these host receptors are critical to elucidating the molecular basis of receptor-mediated spillover events 13.

These molecular interactions determine the threshold of neuroinvasion, in which the unique conformational landscape of glycoprotein ectodomain determines binding strength to neural cell adhesion molecules and retrograde axonal transport efficiency 24. After the ribonucleoprotein complex is released into the cytosol, the virus takes advantage of dynein motor protein machinery to allow efficient long-range retrograde transport along microtubules toward the neuronal soma [3]. Fundamentally, this active translocation event relies on the process of clathrin-coated endocytosis to sequester the virus within luminal endosomal cargoes as it navigates through the axoplasm en route to the central nervous system [25]. Recently, transferrin receptor 1 has been identified [26] as an important host factor that uses clathrin-mediated endocytosis to permit rabies virus entry and trafficking. This protein complex functions as a critical co-factor by engaging with the metabotropic glutamate receptor subtype 2 in clathrin-coated pits, coordinating viral endocytosis with host cell endocytic trafficking pathways [27].

Bookmarking multi-receptor interplay of rabies virus entry into host cells may have allowed the virus to avoid evolutionary pressure against redundancy in its mode of infection. Such receptor heterogeneity allows for successful infection in a wide variety of cell types and host species. This suggests the virus has subverted normal cellular transport systems (recently reviewed for SVDV in Chen et al. [7]). The entry of rabies virus is mediated through a complex network of receptor interactions and endocytic pathways enabling efficient neuroinvasion and intracellular transport. These mechanisms play a major role in the virus's high infectivity and efficient dissemination throughout the nervous system as well.

Neuronal Receptors

The neural cell adhesion molecule and the p75 neurotrophin receptor (p75NTR) act as key surface determinants responsible for the virus's preference for sensory and motor neurons [28, 29]. Moreover, novel data indicate that the metabotropic glutamate receptor subtype 2 (mGluR2) serves as a key entry receptor in the central nervous

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system, and its widespread expression is associated with virus neuroinvasion [27]. Furthermore, viral glycoprotein binding to such a wide range of receptors can also lead to flexibility in the environment of different tissue types, possibly accounting for its ability to infect cells that are not neurons by other pathways such as transferrin receptor 1 clathrin-mediated endocytosis [13, 26]. These multiple entry mechanisms imply that rabies virus tropism is not ascribed to a unique, limited receptor but the ability of the virus to usurp widespread endocytic machinery and membrane-bound signaling molecules [2]. As a result, this complex receptor engagement enables the virus to evade the blood-brain barrier and exploit high-affinity interactions at peripheral nerve terminals prior to invading localized sites of immune privilege within the neural network [30]. Besides retrograde translocation, the virus can also take advantage of anterograde axonal transport routes that are important for centrifugal propagation to the salivary glands followed by spreading to new hosts [3]. Such rapid, G protein-dependent movement occurs at rates an order of magnitude faster than retrograde trafficking enabling the virus to traverse between parts of the peripheral nervous system with relative ease once the CNS has been colonized.

Since rabies virus has been shown to transduce through at least 3 classes of neuronal receptors (including p75NTR, NCAM, and mGluR2), the selective tropisms suggest a highly specialized receptor interaction. This diversity of receptors enables the virus to adapt itself to different neuronal populations, ensuring the successful process of neuroinvasion. Critical role of neuronal receptor specificities in rabies virus neurotropism. The myriads of receptors the virus can interact with increases its ability to infect sensory and motor neurons as well as helping promote the rapid expansion of infected neurons throughout the central nervous system.

Non-Neuronal Receptors

Even though the initial inoculum of virus tends to replicate in muscle cells, the interaction with extraneural receptors affecting local replication prior to retrograde transport is a key determinant as well [20]. disease specifically, the restricted surface expression of certain glycans and proteinaceous receptors on non-neuronal cell membranes establishes a permissive microenvironment enabling early stages within the viral life cycle including initial budding and maturation time between dynein-mediated retrograde transport machinery engagement. Even more impressively, the identification

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of specific cell surface molecules critical for viral internalization in both neuronal and non-neuronal settings represent an elegant exploitation of endogenous trafficking routes present throughout the host [26, 27]. The hijack of transferrin receptor 1-mediated endocytosis is an example of destruction from within, as the virus uses housekeeping cellular processes to access the cytoplasm, regardless of cell type [26]. This reliance on generalized endocytic mechanisms implies that variations in the viral glycoprotein structural plasticity are used to recruit it for duty across different cellular microenvironments, consequently expanding the range of tissue types permissive to primary infection [22, 31]. Furthermore, the capacity of the virus to interact with such peripheral hosts may determine localized incubation times and consequently dictate the kinetics in primary infection at exposure sites [32].

Early outbreaks of replication in peripheral tissues are critical as they increase the viral load necessary to breach the physiological barriers surrounding the neuromuscular junction. Additionally, nicotinic acetylcholine receptor involvement at these junctions has been suggested to draw viral particles into proximity to nerve endings and thereby reduce the threshold for successful neuroinvasion [9]. In addition, integrin-biased proteoglycans stabilize viral adsorption at the neuromuscular junction as nucleoprotein assemblies transition from myocyte beds to presynaptic terminals. These interactions presumably modulate the efficacy of virion internalization by promoting presynaptic membrane fusion with specialized signaling platforms. The capacity of rabies virus to engage with receptors on non-neuronal cells suggests that initial infectious events do not occur solely in neurons. Viral replication may initiate peripherally in tissues like muscle cells prior to invasion into nerve terminals. Thus, these non-neuronal receptors aid in the initial steps of rabies infection facilitating viral replication at peripheral sites. This stage is critical to enhancing viral load pre-neuroinvasion via neuromuscular junctions.

Role of Glycoproteins in Entry

The rabies virus glycoprotein is the principal proxy essential to host cell membrane fusion, coordinating the switch from intracellular endosomal compartment entrapment into cytoplasmic release. In the acidic environment of the endosome, conformational changes in the glycoprotein occur that allow for coalescence of the viral and endosomal membranes [22], initiating this structural rearrangement. In addition,

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these pathogenic strains are known to downregulate glycoprotein surface expression as a means of subversion [30], one which facilitates increased viral replication intracellularly while retaining the capability for efficient dissemination as naked virus and provides protection against host neutralization [31]. In contrast, weakened strains were found to have a strongly enhanced glycoprotein display that benefits the elicitation of neutralizing antibodies but also heightens proqynfqn if respective inflammation. This differential expression likely reflects an evolutionary balance between maximizing neuroinvasiveness and minimizing activation of innate immune sensors, with a counterproductive effect on virulence through the internal milieu and continued propagation of virus within that host [31]. Rabies virus glycoprotein exhibits high structural plasticity beyond such tactics, employing a trimeric pre-fusion conformation to engage diverse host cell surface receptors and facilitate stable binding [33].

This dynamic of stabilization was often exploited by neutralizing monoclonal antibodies that freeze the protein in its pre-fusion state, representing a critical checkpoint for both viral infectivity and candidate therapeutics [33, 34]. In addition, the identification of integrin beta 1 as a further binding partner in skeletal muscle highlights yet another example of how the virus engages the use of a wide variety of cell-surface molecules to facilitate successful host entry [13]. These receptor-mediated interactions are augmented by the ability of the glycoprotein to enhance retrograde axonal transport through neuronal surface protein interaction such as that with the low-affinity nerve growth factor receptor, which directs virion traffic towards the neuronal soma [9, 35]. This glycoprotein is a class III viral fusogenic protein, which means it can work without prior proteolytic cleavage of the protein [36]; hence, instead of driving conformational changes that would otherwise collapse into a metastable homotrimeric assemblage like in other viruses, the virus maintains structural integrity while stretching to insert hydrophobic fusion loops directly into target membranes.

This mechanism has been further elaborated on in recent structural studies, which describe how the trimeric pre-fusion conformation is held together by specific inter-protomer interactions and quaternary epitopes that shield the fusion machinery until an appropriate iterant signal is encountered [33, 37]. Polymorphisms, such as the R333Q substitution, modulate protein antigenicity and pathogenic potential by

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modifying stability of the trimeric structure [24], confirming functional relevance to these structural motifs.

The receptor binding and membrane fusion of the rabies virus is mainly determined by a protein called glycoprotein. Its structural variability and strain-specific differences play a role in viral pathogenicity and immune recognition. Differences between pathogenic and attenuated strains highlight the central role of the glycoprotein in viral virulence. Rabies virus glycoprotein plays crucial roles in receptor binding, membrane fusion and immune evasion. Differences in glycoprotein expression and structure play a major role in dictating viral infectivity, pathogenicity, and vaccine efficacy.

Cellular Tropism of Rabies Virus

Neurotropism retains the firmest depiction of pathogenesis, but general tropism is further illustrated as the virus first utilizes non-neuronal receptors in peripheral tissues to establish a localized reservoir. Such an early phase of replication in the skeletal myocytes and neuromuscular spindles also allow the virus to escape immediate immunological detection, which permits a period of silent amplification before infiltration into the central nervous system [23, 38]. Moreover, infection of non-neuronal cells, such as adrenal medulla or lymphoid tissues, may allow the virus to spread systemically during the prodrome. Additionally, the ability for viruses to utilize divergent host-specific receptors—such as integrin β1 through multiple mammalian species—allows successful cross-species spillover events and highlights the evolutionary plasticity of viral entry routes [13, 39]. Furthermore, evidence suggests that soluble glycoprotein variants can interact with synaptic receptors (e.g. the $alpha$7 nicotinic acetylcholine receptor), to pre-activate target sites ahead of mature virion delivery [29].

Through interactions with all these elements, they effectively modulate the local microenvironment and produce a gradient of receptor occupancy that guides viral particles toward high-density cholinergic locations. Localized receptor recruitment then promotes further sequential engagement of the p75 neurotrophin receptor and neural cell adhesion molecules required for charting the complex topography of the peripheral nervous system. Also correlating with this early phase of neural invasion, the capture

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of host-specific gangliosides is an important factor that augments the glycoprotein's affinity for the axolemma, facilitating a high-fidelity transfer from peripheral sites to central nervous system [20, 34].

In addition, the innate structural plasticity of glycoprotein cytoplasmic tail imparts a second level dependent effect on endocytosis [31], thereby modifying the kinetic profiles of various uptake receptors that operate through different endocytic routes in diverse strains. As depicted, these variable routes of entry ultimately depend on unique cell-type receptor synthesis and expression, necessitating a complex cross-species dance of molecular interactions for neuro-invasion involving NMJs [40]. In particular, the neurotoxin-like motifs of the glycoprotein ectodomain are structurally homologous with components from snake venom and mediate high-affinity interaction with neuronal nicotinic acetylcholine receptors [41]. While rabies virus is predominantly neurotropic, there is increased cellular tropism at the onset of infection. The engagement of peripheral tissues and multiple receptor classes implies that infection is a multistep event involving multiple host cell types. Rabies virus tropism is not limited to neurons, incorporating peripheral tissues that facilitate transmission and gene expression. This more generalized cellular targeting is key to successful neuroinvasion and disease progression.

Axonal Transport and Spread

After initial entry, the virus hijacks the host's retrograde axonal transport machinery to travel through peripheral neurons toward the central nervous system while insulating itself from the immunologically competent surrounding environment [5]. This subcellular traffic is mediated by the selective recruitment of microtubule-associated motors, which relay the virion through long axonal processes and evade detection [42], the sensing of which would through intrinsic virological patterns normally impose antiviral innate immune restrictions in the extracellular compartment. By hitching a ride with these dynein-driven motors, the virus averts lysosomal degradation routes that would otherwise segregate endocytosed cargo, assuring passage of the viral ribonucleoprotein complex to the perikaryon [43] Then, the viral polymerase performs primary transcription directing the synthesis of subgenomic mRNAs encoding essential viral proteins and prudently sequestering this activity in grossly specialized inclusions to avoid recognition by cytoplasmic rnp's double-

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stranded RNA intermediates like RIG-I. In addition to this immune evasion strategy, the viral phosphoprotein also functions to stabilize these transcriptionally active compartments to prevent the premature dissociation of the polymerase complex from template genome.

Rhabdoviruses, including rabies virus, exploit host axonal transport machinery to rapidly traverse long distances within neurons. This strategy gives the virus a means to evade immune detection as it makes its way toward the central nervous system. Retrograde axonal transport is a key pathway for neuroinvasion of rabies virus. Generalized infection of microtubule cargo leads to synergistic recruitment of transport machinery, potentially enabling the virus to spread quickly through neural networks while evading immune clearance.

Impact on Neuronal Function

In addition to being able to evade immune detection, rabies infection also leads to selective and compartmentalized degeneration of axons and dendrites [41], a process recently associated with key depletion of intracellular NAD+ and subsequent activation of SARM1 signaling [42]. This catabolic pathway, though central to the morphological atrophy observed, occurs in the context of an absence of overt structural damage in the neuronal soma or significant neuroinflammation emphasizing a paradox whereby physiological function is extinguished before cellular death [7]. The virus additionally alters neurotransmitter signaling, interfering with serotonin and muscarinic acetylcholine and GABA transmission that propagate further systemic neurological deficits observed along clinical progression [8]. The swift neuro-functional decay is exacerbated by the virus's ability to commandeer its host fast axonal transport machinery, an effective repurposing through which the pathogen traverses retrograde and anterograde routes for systemic dissemination [28]. Moreover, recent transcriptomic data have shown that the observed neurodegenerative changes occur very early in infection cycle and are independent of interactions between neuronal and glial cells [7].

These data suggest that the RABV-driven changes in neuronal excitability, including reduced activation of membrane sodium channels, may be due to these early transcriptional changes in gene expression instead of being solely driven by late

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cytopathic effects [7]. Interestingly, localized downregulation of synaptic proteins suggests that the virus engages in active remodeling of the synaptic proteome to bias towards trans-neuronal spread, thereby allowing the virus to rapidly disseminate through pre-existing neural circuits. In this scenario, the apoptotic viral phosphoprotein serves an important function in regulating the dynamics of host membraneless organelles via liquid–liquid phase segregation that drives the proper spatial distribution of its replication apparatus and contributes to appropriate genome amplification [45]. We suspect that this spatial organization of replication compartments may lend to the disruption of the vesicular synaptic cycle observed, but with a focus on those key regulatory kinases targeted by viruses including casein kinase 2 and protein kinase C which act as bottlenecks to neuronal metabolism [46]. Thus, SARM1 pathway activation during this stage is a clear mechanism for the aforementioned axon disintegration, as viral infection activates such pro-neurodegenerative NADase in an effort to provide sustained and non-destructive tissue breakdown [44, 47].

Rabies virus infection induces severe functional perturbation of neurons but is not always followed by cell death. This remarkable pathogenic strategy enables the virus to manipulate neuronal signaling and behavior whilst retaining the functional neural circuitry needed for viral dissemination. Pathogenesis of rabies involves impairment of neuronal function than destruction. Viral-mediated changes in neurotransmission and axonal structure are related to neurological manifestations during infection

Factors Influencing Tropism and Specificity

The cellular tropism of rabies virus is largely determined by the differential expression of surface receptors in specific neuronal populations, thereby regulating binding and subsequent internalization of the virus [48-49]. The selective affinity for specific networks is also dictated by the reliance of many neurotropic viruses on synapse-rich retrograde transport mechanisms, leading to a precise trans-synaptic trajectory throughout the brain and spinal cord [2]. Additionally, recent high-resolution spatial mapping demonstrated that this neuronal tropism is not only acquired through initial receptor binding, but also maintained by the virus itself through preserving an intact neuronal circuitry to permit efficient multisynaptic dissemination [48]. Recently, improvements to single cell transcriptomics and in situ sequencing have elucidated how

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the virus hijacks these precise synaptic infrastructures, facilitating household immunity escape and trans-neuronal translocation [50]. Furthermore, the addition of 3D human iPSC-derived neuronal models [49] suggests that local microenvironment factors and viral strain diversity strongly influence such tropism profiles in the CNS highlighting thereby an intricate complexity of synaptic vulnerability [51]. The functional selectivity is further enhanced by the differential expression of specific neuronal surface receptors, as well as their associated intracellular trafficking proteins, which ensure that the viral dissemination corresponds to functional neural circuits [28, 46].

Furthermore, the introduction of genetically modified rabies viruses for monosynaptic tracing has shown that this innate tropism could be used to visualize precise neural connectivity provided that the cytotoxicity and transcriptional dysregulation associated with the infection are considered into data interpretation at circuit-level [49, 52]. These methodological refinements — such as the development of double-deletion-mutant systems that enable transient expression of viral genes to reduce long-term toxicity yet retain unique labels for monosynaptic inputs [53] — would require further validation in insect models. Host receptor distribution, viral protein interactions and neuronal network structure determine viral tropism. Molecular mapping methods have made vital inroads into the selective spread of rabies virus through neural circuits. Viral traits contribute to rabies virus tropism, with receptor expression and connectivity among neuron types playing key roles. Together, these parameters shape infection dynamics and disease in the nervous system.

Viral Strain Variations

This variance in neuroinvasive capacity exists between strains, and is often linked to mutations to the glycoprotein gene, which impact viral entry efficiency and subsequent trans-synaptic kinetics [54, 55]. More specifically, engineered variants using chimeric glycoproteins (e.g. the optimized oG sequences) exhibit increased binding avidity and retrograde tracing quality enabling more effective profiling of presynaptic inputs [56]. In addition, pseudotyped systems such as the one using the avian leucosis virus coat protein EnvA and cognate TVA receptor permit USM-viral entry to be restricted to genetically defined cell types [57]. Moreover, carefully titrated helper virus concentrations that will invariably be needed—including the exact rabies glycoprotein and receptor concentrations—still represent a primary limiting factor in

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generating strong monosynaptic labeled circuits [58, 59]. Outside of these limitations designed by nature, the development of novel packaging systems has enabled high-titer vectors such as CVS-N2c-ΔG [60] that make retrograde tracing in previously unreachable neuronal populations order(s) of magnitude more sensitive and scalable [61].

Genetic differences between rabies virus strains have a major impact on viral infectivity and neuroinvasiveness and experimental uses. Combined with engineered strains that have enabled the study of neural connectivity and viral pathogenesis, these approaches including chimeric RSV expressing GFP14 (RSV-GFP14) 2 or potentially our new tool, rRSV-SDC-DP5FANion/ΔNFC — will inform efforts to prevent and treat RSV in humans. Rabies virus strain-specific differences modulate receptor tropism, neuroinvasion, and trans-synaptic spread efficiency. Studying these variants will be critical in optimizing viral tracking tools and devising potentially effective therapeutic strategies.

Conclusion and Future Directions

Future studies MUST combine longitudinal imaging with high resolution, cell type-specific transcriptome profiling of RTs to fully resolve the outstanding ambiguities regarding precise molecular determinants of viral tropism. By tackling the shortcomings of existing viral vectors—especially in terms of long-lasting cell viability and trans-synaptic transfer kinetics—in a systematic manner, these studies will pave the way for a more sophisticated foundation upon which to map the functional structure of mammalian brains [53, 62]. In summary, a description of the balance between viral protein interactions and host cellular mechanisms will need to be elucidated if we are ever to overcome the inherent cytotoxicity which currently limits rabies-based neural circuit analysis in a long-term way [63]. Development of next generation tracers that achieve structural integrity with a minimal neurodegenerative footprint, historically associated with viral propagation [52, 64], will be possible by bridging these mechanistic insights onto newly emerging CRISPR-based intervention strategies. These advances will be significant in moving from descriptive mapping of structural architecture to live functional interrogation of complex neural networks, thereby improving our definition of the synaptic landscapes that underlie cognition and disease. This opens the door to combining these clever tools with novel non-transsynaptic

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anterograde markers, enabling a full-featured and left-right view of neural circuitry free from the limitations imposed by existing paradigms being retrograde only [57]. Furthermore, ongoing optimization of trans-synaptic kinetics will be critical to reducing labeling density variability across neuronal populations. Moreover, the implementation of machine learning-guided design and implementations of M-CREATE presents a viable route for screening synthetic capsids with improved specificity and broader applicability across multiple species [64]. These innovations could be leveraged in future studies alongside retrograde viral platforms to achieve more comprehensive circuit definitions [65, 66] that avoid the constraints of strictly trans-synaptic approaches [67]. Therefore, the design, together with modular approaches to viral platforms that incorporate both retrograde and anterograde tracing capabilities will be key to elucidating the complete topology of cellular interactions within the central nervous system [2, 68].

In addition, because these dual-modality tools can be combined with spatial transcriptomics, the underlying molecular signatures that define neuronal subpopulations organized around specific synaptic architectures will become accessible at an unprecedented resolution. Ultimately, these multi-modal technological weavings will allow for the mapping of dynamic synaptic plasticity, from static connectome maps toward a more causal and physiological understanding of how neural state-dependent processes redirect large-scale circuit flow. Understanding how different rabies virus strains interact with host cells will benefit from convergence of molecular biology, neuroimaging and genetic engineering approaches in future studies. Next-generation technologies like CRISPR-based modifications and advanced viral vectors may revolutionize neural circuit mapping with lessened toxicity for the target area. Further investigation into rabies virus tropism and host interactions will serve to illuminate both therapeutic developments, as well as neuroscience research tools. Those advances, along with improved viral tracing systems and safer viral vectors, will propel the understanding of neural connectivity and viral neuropathogenesis.

Intercellular spread of rabies virus: Efficient entry into the nervous system via receptor-mediated entry and intercellular transport mechanisms Rabies virus has a highly specialized neurotropism. As the virus preferentially infects neurons, it can also interact with non-neuronal cell types during early stages of infection to assist in viral

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amplification before neuroinvasion. Structural proteins of the virus (especially glycoprotein) are important for binding to receptors, mediation of membrane fusion and evasion established immune responses by the host.

Moreover, the virus hijacks cellular transport including dynein-mediated retrograde axonal transport to enter and be protected from immune detection in the central nervous system. In conclusion, the tropism of rabies viruses is a rigid result from complicated interaction between viral genetic characteristics with host receptor distribution and neuronal circuitry construction to promote viral spread and pathogenesis. Characterization of these mechanisms is critical for enhancing therapeutic strategies, vaccine development, and safe application of rabies-derived viral tools in the field of neuroscience. Thus, the major conclusions are summarized as follows:

Rabies virus is a strongly neurotropic pathogen that can selectively infect peripheral neurons and propagate to the brain through retrograde axonal transport. There is redundancy and versatility in viral entry mechanisms; various host receptors that facilitate viral entry include nicotinic acetylcholine receptors, p75 neurotrophin receptors, neural cell adhesion molecules (N-CAMs), and metabotropic glutamate receptors. Peripheral tissues, especially skeletal muscle cells, represent initial replication centers, where the virus spreads before entering in neuronal terminals at neuromuscular junctions. The glycoprotein of the rabies virus is a key determinant of viral infectivity and pathogenicity, mediating receptor binding, endosomal membrane fusion, and immune evasion strategies supporting viral survival in host tissues. Astrocytes and other glial populations are also possible non-neuronal targets of viral infection, modulating immune responses while potentially allowing for the virus to persist within the CNS.

Mechanisms of axonal transport also contribute to viral spread, allowing the virus to travel long distances along microtubules without detection by extracellular immune mechanisms. In its pathogenic process, rabies virus infection impairs neuronal function instead of directly killing neurons and rewires neurotransmission pathways causing the signs and symptoms observed in rabid animal disease.

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Mutations in viral strains can have a major influence on neuroinvasiveness and receptor interactions showing genetic variation of the glycoprotein as well as other aspects of the virus are relevant to its pathogenicity and transmission level. New molecular and imaging technologies are improving our understanding of rabies virus tropism, allowing for better mapping of neural circuits and host–virus dynamics. Further studies should be directed to the enhancement of our rabies based viral tools and therapeutic approaches into safer ones, through the design- either by genetic alteration or by genomically encoded elements- of new vectors (i.e. safe alternative rabies strains) or molecular strategies that could help seine neurotoxicity whilst keeping the potential of tracing given cell-types.

Research Recommendations

1. Explore other host receptors that contribute to rabies virus entry: Future studies may also investigate other, yet-to-be-identified neuronal and non-neuronal receptors that facilitate rabies virus attachment and internalization. Novel host factors associated with viral entry and cellular susceptibility could potentially be identified using advanced molecular methods like CRISPR screening or proteomics.

2. Investigate other types of cells involved in rabies infection: While neurons are the major target cell type for rabies virus, accumulating evidence point to glial cells and other peripheral cell types as potential facilitators of rabies virus replication and immune modulation. More studies are needed to understand how these cells contribute to maintenance of the virus and progression of disease.

3. Interactions of viral glycoproteins: Insights from Molecular mechanisms: Key roles in receptor binding, membrane fusion, and immune evasion are played by the rabies virus glycoprotein. A lot of structural and functional studies will still focus on glycoprotein conformational dynamics and receptor-binding domains to help uncover potential antiviral targets and optimize vaccine design.

4, Enhance the understanding of axonal transport aspects: Further studies would elucidate the interaction of rabies virus with those host cytoskeletal components and motor proteins in retrograde and anterograde transports. This information could inform strategies to prevent viral spread in the nervous system.

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5. Determine mechanisms for neuronal dysfunction upon infection: Future work should examine rabies virus' effects on neurotransmission, synaptic function and neuronal metabolism. It is hoped that a better understanding of the molecular underpinnings of these functional disruptions will translate into more effective therapeutic strategies for limiting neurological injury.

Future Perspectives

1. Advances in rabies-based viral vectors for neuroscience: The rabies virus is a gold standard tracer of neural circuits. Advances in viral vector technology will pave the way for more selective and less cytotoxic tools to map brain circuitry in greater detail.

2. Incorporation of new technologies for rabies studies: Emerging technologies including single-cell transcriptomics, spatial transcriptomics, and high-resolution brain imaging will yield new information about the tropism of viruses as well as host–virus interactions on a cellular level.

3. Application of gene-editing technologies: CRISPR-based approaches have the potential to facilitate the design of rabies viral vectors modified to exhibit antropleotropic targeting or host-targeted therapies that disrupt a strategy during viral replication or cellular entry.

New antiviral and therapeutic strategies development

Targeting viral proteins including glycoproteins and polymerase complexes that are critical for replication or spread will be important in moving forward with antiviral drug design as well as fibre and receptor targeted gene therapies. Improved understanding of cross-species transmission. Since rabies virus infects a broad range of mammals, characterizing the dynamics of viral adaptation across hosts will improve predictability for spillover events as well inform public health prevention efforts.

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