Chapter

Morbillivirus Replication and Immune Evasion: Implications for Vaccine Design

Ashok Kumar, Ram Kumar, Anil Gattani and Sanju Mandal

Abstract

Morbillivirus, a genus within the Paramyxoviridae family, includes critical human and veterinary pathogens such as the measles virus, canine distemper virus (CDV), rinderpest virus (RPV), and peste des petits ruminants virus (PPRV). The understanding of morbillivirus replication, which encompasses viral attachment, fusion, transcription, replication, and virion assembly, is fundamental for advancing therapeutic interventions. The complex interplay between proviral and antiviral cellular signaling pathways, including those regulating innate immune responses and apoptosis, is central to both viral pathogenesis and host immune evasion. Morbilliviruses deploy various immune evasion strategies, such as the suppression of type I interferon responses, to establish persistent infections. Delineating these molecular mechanisms is critical for optimizing vaccine development and designing antiviral therapeutics, particularly in response to emerging viral strains. This chapter explores morbillivirus replication dynamics, immune evasion tactics, key signaling pathways, and recent advancements in vaccine and antiviral therapeutic strategies for managing these pathogens in human and veterinary populations.

Keywords: morbillivirus, viral replication, immune evasion, signaling pathways, vaccine development

1. Introduction

Morbilliviruses belong to the order *Mononegavirales*, the family *Paramyxoviridae*, and the subfamily *Paramyxovirinae*, known as pleomorphic, enclosed, negative-sense, single-stranded RNA viruses that replicate intracytoplasmically [1, 2]. Measles virus (MV), rinderpest virus (RPV), peste des petits ruminants virus (PPRV), canine distemper virus (CDV), cetacean morbillivirus, phocine distemper virus, and feline morbillivirus are the seven known members of the genus morbillivirus [3]. Both humans and animals infected with the morbillivirus experience severe immunosuppression [4], although those who survive often acquire lifetime immunity [5]. It is thought that different morbillivirus prototypes exhibit cross-protection. Viruses require more than just raw ingredients for nucleic acid and protein synthesis to

spread successfully within their host. While research has focused on particular host components used by viruses, there is still a lack of quantitative functional insights for all host factors needed for viral reproduction. Viruses employ the host cell's machinery to replicate themselves, creating "viral factories" through protein-RNA and protein-protein interactions [5]. Viral pathogenicity and host range are determined by molecular interactions with cellular components. High-throughput sequencing and proteomics technologies have discovered hundreds of host components essential for virus replication, providing insights into potential targets for antiviral medication development [6].

2. Genome organization

Pleomorphic, enclosed, negative-sense, single-stranded viruses that replicate intracytoplasmically are known as paramyxoviruses. In animals, this family causes multisystemic, neurological, and respiratory disorders. A single strand of RNA, somewhat less than 16 kbp in length, makes up the genomes of morbilliviruses. The six structural proteins—the nucleocapsid (N), the phospho (P), the matrix (M), the fusion (F), the hemagglutinin (H), and the large (L) proteins—are encoded by the six contiguous, nonoverlapping transcription units into which they are arranged [7]. The latter is the viral RNA-dependent RNA polymerase. Their 3′ (leader) and 5′ (trailer) terminal extremities include highly conserved regions that function as transcription and replication promoters **Figure 1**. Sequences extending into the untranslated area at the beginning of the N gene open reading frame (ORF) and the untranslated region at the end of the L gene ORF are examples of full promoter elements. All

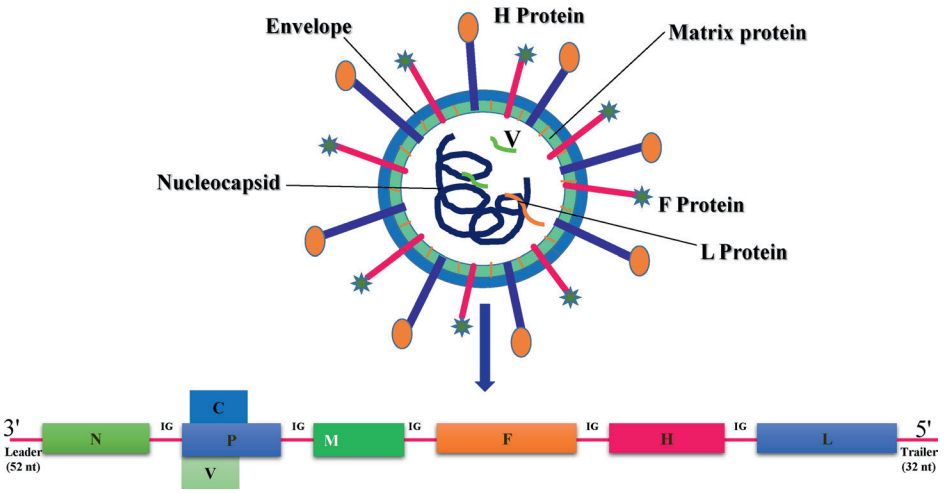

Figure 1.
Schematic diagram of a Morbillivirus, Genome arrangement of virions are enveloped and pleomorphic in shape which varies in size from 150 to 700 nm (Mean size 500nm). The virions contain a negative-strand RNA genome enclosed in a ribonucleoprotein (RNP) core. The genomic RNA is packaged by nucleoprotein (N) to form nucleocapsid along with phosphoprotein (P) and large protein (L). The virus genome is ~16kb in length (15948 nts) which consists of six structural (N, P, M, F, H and L) and two non-structural (V and C) proteins. At the 3' and 5' ends, there are untranslated regions of 52 nt and 32 nucleotide, respectively. IG = Intergenic Region, N = Nucleocapsid Protein, P= Phosphoprotein, M = Matrix Protein, F = Fusion Protein, H = Hemagglutinin Protein and L = Large Protein (Polymerase).

of the cis-acting signals required for initial transcription and the creation of a complete positive-sense RNA genome copy, which is necessary for the synthesis of new genome RNA, are found in these locations. Each mRNA transcription unit has semiconserved start-stop sequence motifs at the beginning and end: (UCCU/C) at the beginning of the transcription and a sequence rich in U residues at the end that indicates the polyadenylation of the mRNAs. An intergenic triplet, often GAA, sits between the end of one transcription unit and the beginning of the next. Upstream mRNA termination is necessary for downstream mRNA synthesis. The RNP core, the transcription/replication unit of the virus, is made up of the N, P, and L proteins as well as the genomic RNA. During the budding process, the host cell produces a lipid envelope that contains the F and H glycoproteins [8]. The two components that make up the budded virion are brought together by the nonglycosylated M's interaction with the cytoplasmic domains of the membrane-associated F and H proteins as well as the nucleocapsid RNPs that are created in the cytoplasm during replication. For viral budding to be effective, the M protein is required. Morbilliviruses produce two nonstructural proteins (C and V), which are encoded in the P gene transcription unit. Ribosomes that scan past the first AUG codon and begin at the second, which is located approximately 20 nt downstream, translate the first of these, the C protein. This protein has no antigenic connection to the P protein and is in a separate reading frame [9]. By adding a nontemplated G residue to around 50% of the P mRNAs, alternative transcription of an mRNA from the P transcription unit yields the second nonstructural protein, the V protein. About halfway up the P protein ORF, the additional Gs are inserted in a particular, highly conserved region called the editing site (5′ UUAAAAAGGG[G]CACAG). Since manmade transcription systems do not exhibit this so-called editing process, it is a characteristic of the viral polymerase. The V protein, a chimeric protein made up of the N-terminus of the P protein and a new, shorter C-terminus rich in cysteine residues obtained from the template sequence in the third reading frame, is produced when this mRNA is translated. Because its coding region is situated before the editing point in P, the V mRNA can also translate the C protein [10].

In addition to regulating transcription and replication, the nonstructural proteins help viruses evade the host's innate immune responses. Morbilliviruses must have a genome length that is divisible by six (the "rule of six"), just like certain other paramyxoviruses [11]. The reason for this need is that each N protein monomer binds to precisely 6 nt, and effective transcription and/or replication are only possible if the complete RNA genome is encapsulated by the N protein. For MV, RPV, and CDV, reverse genetics methods have been developed. This makes it possible for a virus to be "rescued" from a copy of its genome, which can then be altered to create viral mutants [12]. These may be used to investigate the molecular underpinnings of host range and pathogenicity, as well as to ascertain the roles of different proteins and sequence patterns.

3. Virus replication

3.1 Infection and virus attachment

The virus's pathogenesis and host susceptibility are heavily influenced by the initial phase of infection, which involves attaching to host cells and delivering the nucleocapsid into the cytoplasm. The PPRV initially interacts with the host

by attaching to cellular receptors *via* its attachment protein, the HN protein [13]. Morbilliviruses effectively reproduce in lymphocytes after first targeting lymphoid tissues. The molecule that signals lymphocyte activation (SLAM), the main cellular receptor for morbilliviruses is also known as CD150 **Figure 2**. The viruses have great lymphoid cell tropism since it is only expressed in immune cells [14]. Signaling molecule for lymphocyte activation by screening a cDNA library obtained from B95a cells, which are extremely permissive for MV [15, 16], discovered SLAM for the first time. When a single clone of marmoset B (B95a) cells was transfected, 293 T cells which are

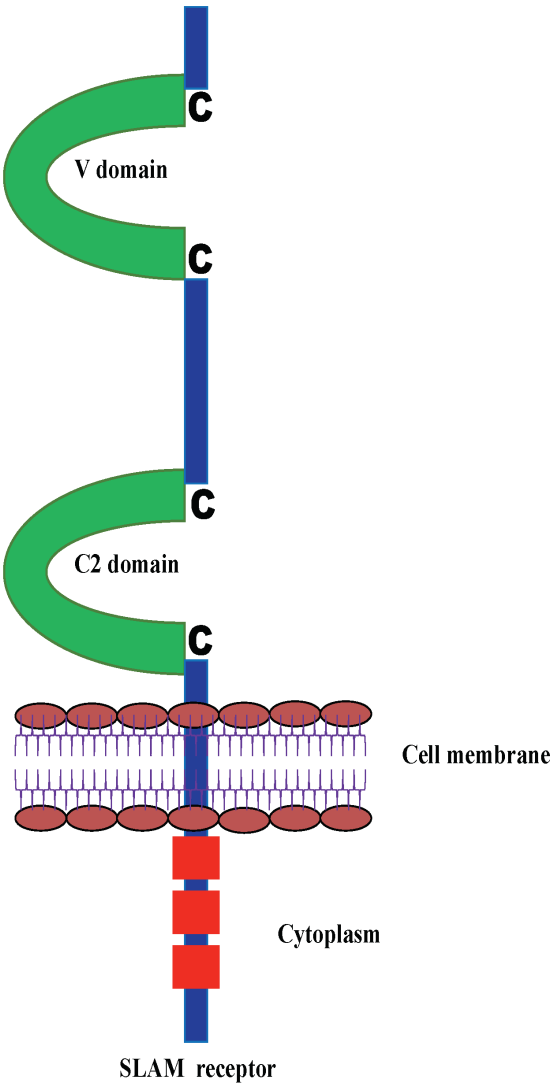

Figure 2.
Schematic diagram of SLAM receptor molecule*: The extracellular domain is composed of a variable (V) and a constant (C2) Ig-like repeat. Its cytoplasmic domain contains three tyrosine residues (red block) that are surrounded by SH2 domain binding sequences. The morbillivirus H protein binds to the V domain on the target cells, which triggers viral infection.*

normally nonsusceptible became susceptible to the vesicular stomatitis virus pseudotype that carries the MV H protein. Lymphocytes, monocytes, dendritic cells, and macrophages are the main cells that express SLAMs [17]. Since SLAMs control T cell activation and can also control the activities of natural killer and dendritic cells, they play a wide role in the modulation of both innate and acquired immune responses [17, 18]. Every morbillivirus attaches itself to SLAM's V domain. The adapter molecules connected to the cytoplasmic tail of SLAM are the SLAM-associated protein (SAP) or EWS/FLI-1-activated transcript 2. Another SLAM molecule in the nearby cells may form an association with the extracellular domain of SLAM. When SLAM engages, it binds to SAP and initiates downstream signaling that causes T helper 2 cytokines to be upregulated [16]. SLAM interacts with the following MV-H protein residues: I194, D505, D507, Y529, D530, T531, R533, H536, Y553, and P554 [19]. A morbillivirus's complete pathogenicity requires SLAM-mediated cell entrance. The recombinant SLAM-blind lapinized strain of RPV is highly virulent in rabbits and has similar pathogenicity to virulent RPV in cattle, making it a suitable model for studying RPV's *in vivo* pathogenicity [20].

A virus's host range and tissue tropism are determined by its cellular receptors. SLAMs found in humans, dogs, cattle, and goats serve as shared receptors for measles virus MV, CDV, RPV, and PPRV [21, 22] found that monkey cells expressing goat SLAM are more sensitive to PPRV separation from clinical material than those expressing cow SLAM. B95a cells are commonly used to isolate MV, CDV, RPV, and PPRV due to their high surface expression of SLAM [15]. Morbilliviruses infect epithelial cells of the intestines, liver, lungs, trachea, bronchial tubes, oral cavity, esophagus, pharynx, and bladder without SLAMs, indicating the presence of alternate cellular receptors. *In vitro* studies have shown that morbillivirus can cause cytopathology and virus generation in SLAM-negative cell types, including epithelial and neuronal cells.

Paramyxoviruses initially infect the upper respiratory tract epithelium from the luminal side before spreading to lymphatic cells [23]. A novel model suggests that wild-type MV spreads throughout the body by infecting SLAM-expressing lymphatic cells, rather than requiring initial virus amplification in respiratory epithelial cells [16, 23]. Infecting rhesus monkeys with an epithelial receptor-blind MV, which does not recognize epithelial receptors but maintains SLAM-dependent entrance, resulted in virulence but no virus shedding, indicating the importance of additional cellular receptors in virus dispersion [24]. Two different research groups identified a novel morbillivirus receptor, PVRL4 (Nectin-4), expressed on epithelial (i.e., I456, L464, L482, P497, Y541, and Y5430) [24, 25]. The Nectin family proteins have three Ig-like loops (V and two C2-type domains) in their extracellular domain **Figure 3**. Nectin-4 is the sole member of the Nectin family that acts as an epithelial cell receptor [13, 26–28]. The other three members do not. After systemic infection, infected lymphocytes and dendritic cells may spread the virus to epithelial cells *via* Nectin-4 on the basolateral side. Morbilliviruses can be found in endothelial and neuronal cells, in addition to lymphocytes and epithelial cells [20]. According to Sato, MV, and CDV cause persistent encephalitis due to their significant neural cell tropism and lack of expression of SLAM and Nectin-4. Morbillivirus cell entrance can occur without SLAM, CD46, or Nectin-4 in several cell lines [23, 29]. This book chapter suggests the presence of other receptors. According to Fujita, heparin-like glycosaminoglycans, cellular cyclophilin B, and CD147 may act as morbillivirus receptors in cells. Both SLAM and Nectin-4 have been linked to PPRV entrance into host cells. While SLAM

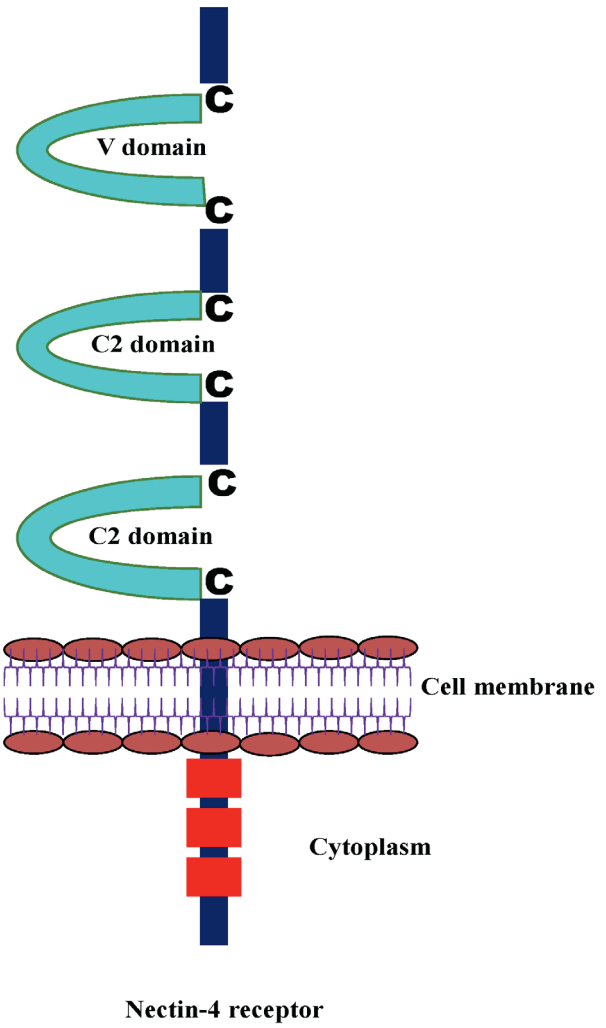

Figure 3.
Schematic diagram of Nectin-4 receptor molecule*: The extracellular domain is composed of a variable (V) and a two constant (C2) Ig-like repeat. Its cytoplasmic domain contains three tyrosine residues (red block) that are surrounded by SH2 domain binding sequences. The morbillivirus H protein binds to the V domain on the target cells, which triggers viral infection.*

is crucial for initial engagement, Nectin-4 acts as an exit receptor to spread the virus throughout the body and promote its amplification and release through various secretions [13, 30, 31].

3.2 Virus entry

Paramyxoviruses typically cause lytic infection in cell cultures. However, high-titer virus yields require adaptation through the selection of mutants that can replicate in the *in-vitro* system. Syncytia are common in paramyxovirus infections in non-polarized cell cultures, but less so in polarized systems. Syncytia are also present in some, but not all, paramyxovirus infections in animals [32, 33]. Paramyxovirus infections are

characterized by acidophilic cytoplasmic inclusions made of ribonucleoprotein structures. Morbilliviruses, on the other hand, produce acidophilic intranuclear inclusions made of nuclear elements and N protein. Paramyxoviruses with the HN protein exhibit hemadsorption. The paramyxovirus fusion (F) proteins mediate viral penetration by fusing the virions' envelope with the host cell plasma membrane, which happens at neutral pH. *Morbillivirus* entry principally depends on the H and F proteins [32] that closely associate to facilitate membrane fusion at a neutral pH. The result of the fusion reaction is that the nucleocapsid is delivered to the cytoplasm. Later in infection, the F proteins produced at the plasma membrane of infected cells can facilitate fusion with nearby cells to generate syncytia (giant cell development), a cytopathic impact that can lead to tissue necrosis *in vivo* and may also be a virus dissemination mechanism. Sialic acid, an acyl derivative of neuraminic acid, is found in both glycoproteins and lipids (sialoglycolipids or gangliosides). Gangliosides operate as both an attachment factor and a receptor for the Sendai virus [34]. The cellular receptor for the morbillivirus measles virus is the cell surface protein CD150SLAM, and the cellular receptor for pneumoviruses, though not proven, appears to involve binding to glycosaminoglycans containing the disaccharide heparan sulfate and chondroitin sulfate B. The M protein shell in the viral particle is thought to have multiple interactions with the nucleocapsid [35]. When the viral envelope fuses with the cell's plasma membrane and the nucleocapsid is released into the cytoplasm, a mechanism must exist to disrupt the M-N connections.

3.3 Virus RNA replication and transcription

Morbillivirus RNA replication and transcription occur within the cytoplasm. Infecting virions include RNA-dependent RNA polymerase (RdRp), which stimulates the synthesis of mRNA and complementary RNA. Transcription begins when RdRp binds to the GP on genomic RNA [7]. The transcriptional units (coding sequence and noncoding surrounding regions) are produced in a start-stop' manner. The RdRp can access a downstream transcriptional unit only when the preceding unit is fully synthesized. RdRp can detach from the template (IG) and restart transcription at GP, allowing for control over the amount of protein generated. The N protein is highly transcribed due to its proximity to the GP. The L protein with the lowest transcription rate is positioned farthest from the GP. Paramyxoviruses transcribe specific mRNA species as naked RNA. The virus-encoded polymerase caps the 5′ end and polyadenylates the 3′ end, making the RNA stable and efficient for translation by host ribosomes [7]. The mRNA transcript contains polyadenylation signals (UUUU) before each IG region, as reported by Munir et al. [36]. Unlike other viral transcripts, the morbillivirus P gene generates three distinct proteins: P, a structural protein, and C and V, nonstructural proteins. According to Munir, the first initiation codon creates the P protein, while the second start codon produces the C protein *via* an alternate reading frame. The absence of the first AUG in the ideal Kozak consensus sequence (A/GXXAUGG) hinders protein synthesis efficiency [37]. Cotranslational editing adds one or more G residues to the P mRNA at a conserved editing location (3 ′-AAUUUUUCCCGUGUC-5 ′) to produce the mRNA for the V protein [38]. The RdRp changes to produce complementary RNA (antigenome RNA) at some point after the mRNA is synthesized. cRNA and the N protein are linked, much as genomic RNA. One theory holds that the RdRp function is switched from mRNA to cRNA synthesis due to the accumulation of unassembled N protein in the cytoplasm [39], while another theory postulates the existence of two distinct forms of RdRp, one for transcription and one for replication [40].

3.4 Virus assembly and release

New paramyxovirus particles are created when the surface glycoproteins, M protein, and ribonucleoproteins (RNPs) assemble at the plasma membrane and then bud. Not much is known about how the morbillivirus assembles and releases. Paramyxovirus assembly and release are significantly influenced by the M protein. By binding with nucleocapsid at virus assembly sites, it acts as an adapter to connect the structural elements of the virions (viral glycoproteins and RNPs) with cellular membranes. It also promotes the incorporation of genomic RNA into budding virions. While M is the primary protein in charge of paramyxovirus assembly and release, additional viral proteins including H, and a number of host variables have also been suggested, along with F and C. Viral components agglomerate at distinct locations on cellular membranes, followed by host cell membrane protrusion, in the precise and intricate process of viral protein assembly. Lipid rafts can serve as platforms for virus assembly because they are abundant in sphingolipids and cholesterol, which have a rigid, structured structure with little flexibility [10, 41]. Instead of being equally distributed across the cell surface, RNA virus envelope glycoproteins are grouped within the membrane microdomains of lipid rafts to create the budding nucleation sites [10]. The raft microdomains are the specific target of paramyxovirus glycoproteins. In certain viruses, both glycoproteins can attach to the rafts, while in others, only the F protein—not the H protein—has the inherent capacity to be integrated into membrane rafts [42]. Other viral components, including the N [43] and M proteins [44], can also attach to the lipid raft microdomains in addition to the glycoproteins. Multiple membrane microdomains can coalesce as viral components accumulate at cell membranes, allowing viruses to construct their own platforms for assembly [10]. In addition to serving as locations for assembly, the raft domains enhance the freshly generated paramyxovirus particles' contagiousness. Paramyxovirus particles form when all structural components of the virus are assembled at specific sites on membranes. These particles bud and pinch off to spread the infection to new cells/hosts [45]. Some paramyxoviruses, including MV and SV, require lipid rafts for assembly but not for budding.

3.5 Virus budding

Enveloped viruses create membrane protrusions, followed by membrane scission and liberation from infected cells. In addition to viral-host protein interactions, viral proteins interact with membrane lipids to induce membrane curvature and fission [46]. Paramyxovirus budding is primarily driven by the M protein, which binds and oligomerizes beneath the plasma membrane. This causes membrane distortion and curvature development. Harrison et al. [47] and Takimoto and Portner [48] have identified multiple methods for paramyxovirus budding. The L domain of paramyxovirus M proteins, also known as P[T/S]AP, PPxY, or YxxL, plays a role in late budding. The L domain interacts with the Endosomal Sorting Complex Required for Transport (ESCRT) system proteins and promotes membrane fission, resulting in the release of virus particles from the plasma membrane. Paramyxovirus budding can occur through ESCRT-dependent [49] or independent [50] pathways. SV budding is well characterized among paramyxoviruses [51]. The ability of the SV-F protein to form a bud depends on a TYTLE motif in the protein's cytoplasmic tail [52], indicating that this motif is required for efficient binding. The cytoskeleton may play a role in paramyxovirus budding, as evidenced by the presence of actin associated with SV

and mutations in the actin-binding domain of the SV-F protein that reduces SV-like particle production. El Najjar et al. [45] found that the cytoplasmic tail domains of glycoproteins have a role in the budding process of paramyxoviruses, in addition to other exocytic components. Glycoprotein clustering in lipid raft microdomains pulls on the plasma membrane, causing initial deformation and further elongation by M protein oligomerization [53] to promote virus budding. Although the intrinsic glycoprotein targets the basolateral surface of polarized epithelial cells, the M protein directs budding to the apical surface. M's loss of apical targeting and surface [41, 54, 55], promotes cell-cell fusion at the expense of virus generation.

4. Immune evasion strategies of paramyxoviruses

Immune evasion plays a crucial role in the pathogenicity of paramyxoviruses, presenting significant challenges in the development of effective vaccines and therapeutics. Paramyxoviruses employ various strategies to subvert both innate and adaptive immune responses, including modulation of host-cell interactions and immune suppression. The following key mechanisms of immune evasion are used by paramyxoviruses, with particular focus on their impact on both innate and adaptive immunity.

4.1 Evasion of innate immunity

Innate immunity is the body's first line of defense against viral infections. This defense system involves the activation of pattern recognition receptors (PRRs) like Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs), which detect viral RNA and trigger the production of type I interferons (IFNs) and pro-inflammatory cytokines. Despite this, paramyxoviruses have evolved several mechanisms to circumvent these immune responses.

4.1.1 Suppression of antiviral pathways

C Protein and accessory proteins interfere with the activation of other innate immune sensors, such as RIG-I and TLRs, which are responsible for detecting viral RNA and initiating antiviral signaling pathways [56, 57].

4.1.2 Interferon (IFN) antagonism

The inhibition of the host's interferon response is a central immune evasion strategy of paramyxoviruses. Viral proteins produced by paramyxoviruses inhibit the activity of interferons and downstream antiviral pathways, preventing the effective initiation of the immune response.

The V protein plays a crucial role in antagonizing IFN production. It inhibits Melanoma Differentiation-Associated protein 5 (MDA5), a cytoplasmic RNA sensor, preventing the activation of type I IFN production. Additionally, the V protein blocks the phosphorylation and activation of interferon regulatory factors (IRFs), which prevents the transcription of interferon-stimulated genes (ISGs) [58–60].

Signal transducer and activator of transcription 2 (STAT2) inhibition: The V protein also targets and degrades STAT2, a key component of the IFN response. In CDV, STAT2 plays a more significant role in IFN responses than STAT1, and its inhibition by

the V protein is essential for the virus's ability to evade immune detection [61–63]. By disrupting the STAT2-IRF complex, the virus effectively disables the host's antiviral response.

4.1.3 Additional mechanisms of immune evasion

Complement system evasion: Some paramyxoviruses produce proteins that inhibit complement activation, preventing immune-mediated lysis of infected cells and enhancing viral persistence [64].

Immunosuppressive cytokine production: Certain paramyxoviruses induce the production of immunosuppressive cytokines like interleukin-10 (IL-10), which inhibit immune activation and promote immune tolerance, further aiding in viral persistence [65].

4.2 Modulation of adaptive immunity

4.2.1 Lymphocyte interference

Paramyxoviruses target lymphocytes, such as T cells and dendritic cells, disrupting the adaptive immune response. Viruses like CDV and MV use viral F and H proteins to mediate fusion with host cells, targeting immune cells *via* specific receptors, such as SLAM (CD150) and CD46 found on T cells, B cells, dendritic cells, and macrophages [21, 66]. By infecting myeloid dendritic cells (BDCA-1+ and BDCA-3+), paramyxoviruses impair the ability of these cells to present viral antigens and activate T cells, weakening the adaptive immune response [67]. This leads to T cell suppression, making the host more vulnerable to secondary infections, as seen in MV infections. Infecting T cells leads to decreased cytokine production and activation [21, 66, 68]. This further contributes to immune suppression, promoting viral persistence and increasing susceptibility to secondary infections, as observed in MV infections, where a compromised immune system predisposes individuals to other infections.

4.2.2 Antibody escape mechanisms

Paramyxoviruses have developed strategies to evade neutralizing antibodies, a key part of the adaptive immune response:

Antigenic variation: The viral F (fusion) and H (hemagglutinin) glycoproteins undergo structural changes that reduce the binding affinity of neutralizing antibodies, allowing the virus to evade antibody-mediated neutralization [69]. This variation supports viral persistence and reinfection.

Fusion/Entry complex adaptation: The F protein undergoes conformational changes to facilitate fusion with host cells and reduce the binding affinity of neutralizing antibodies, helping the virus continue to spread while evading immune detection [69].

Antibody-mediated enhancement (ADE): Antibody-mediated enhancement (ADE) in paramyxoviruses occurs when non-neutralizing antibodies facilitate viral entry into immune cells, such as macrophages, by binding to Fc receptors. This process enhances viral infection, leading to increased replication and potentially more severe disease. While ADE has been observed in some paramyxoviruses, such as respiratory syncytial virus (RSV), it is less commonly seen in others like measles [70–72]. In these cases, suboptimal antibody responses or prior exposure can increase the risk of ADE. Despite this, paramyxoviruses generally elicit strong immune responses, and the risk of ADE is relatively low, particularly with effective vaccination. Nonetheless,

understanding ADE in paramyxoviruses remains important, especially in cases of incomplete immunity or suboptimal vaccine responses [70].

In conclusion, paramyxoviruses employ a wide array of sophisticated immune evasion strategies to overcome both innate and adaptive immune defenses. These strategies include the inhibition of interferon production, suppression of antiviral pathways, disruption of lymphocyte function, and evasion of antibody-mediated neutralization. By targeting key immune mechanisms, such as interferon signaling and dendritic cell function, paramyxoviruses can persist in the host and evade immune surveillance. Although antibody-dependent enhancement (ADE) is relatively rare, it remains an important consideration, particularly in cases of incomplete immunity or suboptimal vaccination. A deeper understanding of these immune evasion tactics is crucial for the development of more effective vaccines and antiviral treatments to combat paramyxoviral infections.

5. Vaccines

Vaccination strategies have played a pivotal role in mitigating the impact of many of these pathogens, although challenges remain in developing vaccines that are both universally applicable and capable of addressing emerging viral variants.

5.1 Types of paramyxovirus vaccines

Vaccines for paramyxoviruses can be broadly categorized into several types based on their composition and mode of action. The categories of paramyxovirus vaccination are addressed as follows. Each vaccine type presents distinct advantages and drawbacks, depending on the viral target, the environmental conditions of vaccine deployment, and the desired immune response.

5.1.1 Inactivated vaccines

Inactivated vaccines consist of viruses that have been chemically or physically inactivated, rendering them noninfectious while retaining their immunogenic properties. These vaccines typically require the inclusion of adjuvants to enhance immune responses. Although inactivated vaccines are general considered safe, they tend to induce shorter-duration immunity compared to live-attenuated vaccines and often necessitate booster doses. For example, the inactivated PPRV vaccines offer effective control of outbreaks but are associated with limited long-term immunity [73]. Likewise, the NDV (B1 strain) is also widely used in regions where live vaccines may pose a higher risk. These inactivated vaccines are safe but induce weaker immune responses compared to their live-attenuated counterparts **Table 1** [74–76]. Advantages and disadvantages of different paramyxovirus vaccine types. Limitations: Short-lived immunity, reliance on adjuvants, lack of differentiating infected from vaccinated animals (DIVA) capability.

5.1.2 Live-attenuated vaccines

Live-attenuated vaccines utilize viruses that have been weakened through serial passage or genetic modification to reduce pathogenicity. These vaccines generally induce robust immune responses, including both humoral and cellular immunity, and

Vaccine type	Advantages	Disadvantages
Inactivated Vaccines	• Low risk of reversion to virulence • Safe for immunocompromised populations • Stable in storage	• Immunity is short-lived • Requires adjuvants • No DIVA capability • Boosters needed
Live-Attenuated Vaccines	• Provides long-lasting immunity • Induces strong humoral and cellular immune responses • Mimics natural infection	• Risk of reversion to virulence • Requires cold storage • No DIVA capability • Risk in immunocompromised individuals
Thermostable Vaccines	• Stable at varying temperatures • Suitable for areas with limited refrigeration • Ideal for low-resource settings	• Efficacy may be affected by poor storage • Still needs temperature control
Recombinant Vaccines	• Safer than live-attenuated vaccines • DIVA capability • Lower risk of adverse reactions • Flexible production	• Reduced efficacy in some cases • Some are still under development for certain pathogens
Virus-Like Particles (VLPs)	• Noninfectious • Mimics virus structure • Safe and does not require biocontainment • Strong immune response like a natural infection	• Still in development • Immunogenicity can vary • Expensive production
mRNA Vaccines	• Rapid development • No infection risk from the vaccine • Can adapt to emerging pathogens • Broad applicability across viruses	• Requires ultra • Cold storage • Limited real-world experience • New technology
Chimeric Vaccines	• Immunity to multiple viruses • Allows DIVA • Can address co-infections	• Potentially short-lived immunity • Requires further optimization and research
Subunit Vaccines	• Safe (no live virus) • Lower risk of adverse reactions • Targets specific viral proteins	• Requires adjuvants • May not offer long-lasting immunity • Requires booster doses

Table 1.
Advantages and disadvantages of different paramyxovirus vaccine types.

often provide long-lasting protection. However, concerns regarding the reversion of the virus to a virulent form and the requirement for cold storage pose challenges.

For example, PPRV (Live-attenuated) vaccines offer long-lasting immunity but are thermolabile and require stringent cold chain management [73]. Similarly, the NDV (La Sota strain) is a well-established vaccine in poultry, which induces strong immune responses but carries the risk of virus reversion to virulence [75]. The CDV (Rockborn and Schneider strains) were commonly used to prevent distemper in

canines these vaccines provide effective protection but may present risks in certain immunocompromised populations [77].

Advantages: Durable immunity, mimics natural infection, robust immune response.

Limitations: Risk of reversion to virulence, storage requirements, no DIVA capability.

5.1.3 Thermostable vaccines

Thermostable vaccines are designed to maintain their efficacy under varying temperature conditions, making them suitable for use in regions with limited access to refrigeration. These vaccines are particularly important for the distribution of vaccines in remote areas or low-resource settings.

For example, I-2 vaccine for NDV, is a thermostable live-attenuated vaccine that is resistant to temperature fluctuations, ensuring its viability during transport and storage in areas with inadequate cold chain infrastructure [74, 75].

Advantages: Stability under fluctuating temperatures, ideal for regions with limited refrigeration.

Limitations: Efficacy may vary depending on environmental conditions, storage still requires temperature control.

5.1.4 Recombinant vaccines

Recombinant vaccines involve the genetic engineering of viral antigens into vectors, typically attenuated viruses, to stimulate an immune response without the risks associated with live viral infections. These vaccines can enable DIVA, which is crucial for distinguishing between infected and vaccinated animals.

For example, the PPRV (Recombinant Vaccines using MVA, Baculovirus) [73], NDV (Fowlpox virus-based recombinant vaccines) [75], and CDV (Recombinant vaccines combining live and inactivated strains) [77].

Advantages: Safer than live-attenuated vaccines, DIVA capability, reduced risk of adverse reactions.

Limitations: Reduced efficacy in certain cases, ongoing development for specific pathogens.

5.1.5 Virus-like particles (VLPs)

Virus-like particles are molecular structures that mimic the architecture of a virus but lack viral genomic material, rendering them noninfectious. VLP vaccines (e.g., the NDV VLPs [75] and PPRV VLPs [73]) have the potential to elicit strong immune responses similar to natural infection, without the associated risk of live virus transmission.

Advantages: Safe, noninfectious, mimics natural virus structure, no requirement for biocontainment facilities.

Limitations: Still under development, variable immunogenicity.

5.1.6 mRNA vaccines

mRNA vaccines utilize synthetic messenger RNA that encodes viral antigens, which are then expressed in the host cells to stimulate an immune response. This

technology allows for rapid vaccine development, as demonstrated by the success of mRNA vaccines against SARS-CoV-2, and is now being explored for various paramyxoviruses (e.g., HRSV Moderna's mRNA-1653) [78] and PIV3 and HMPV mRNA vaccines [78].

Advantages: Rapid development, adaptability to emerging pathogens, and no risk of infection from the vaccine.

Limitations: Limited real-world experience, requires ultra-cold storage, and relatively new technology.

5.1.7 Chimeric vaccines

Chimeric vaccines are genetically engineered to combine components from different viruses to create a hybrid vaccine capable of inducing immunity against multiple pathogens (e.g., the RPV- PPRV Chimeric Vaccine [73]). These vaccines may also facilitate DIVA, offering an advantage in surveillance and control efforts.

Advantages: Immunity to multiple viruses, enables DIVA.

Limitations: Potentially short-lived immunity, requires additional research for optimization.

5.1.8 Subunit vaccines

Subunit vaccines For example, the HeV and NiV (glycoprotein-based subunit vaccines) and RSV (HRSV subunit vaccines) [79, 80] consist of purified viral proteins, typically glycoproteins, which are sufficient to stimulate an immune response without using the whole virus. These vaccines are particularly valuable for pathogens that pose significant safety risks, as they eliminate the need for live viral material.

Advantages: Safe, no live virus, reduced adverse reactions.

Limitations: Requires adjuvants, may not provide long-lasting immunity.

The development of vaccines for paramyxoviruses has made significant strides, with various vaccine platforms now available or under development. While live-attenuated vaccines remain the most widely used due to their efficacy, novel vaccine strategies such as recombinant, mRNA, and virus-like particle-based vaccines show promise in addressing some of the limitations of traditional approaches. The continued advancement of these vaccine technologies is crucial for enhancing global efforts to control paramyxovirus-related diseases, particularly in regions with limited healthcare infrastructure.

5.2 Challenges in vaccine development

The development of vaccines for paramyxoviruses faces several scientific and practical challenges despite notable progress. One significant hurdle is the variability in vaccine efficacy, as the effectiveness of vaccines can differ depending on the circulating viral strains. For instance, the La Sota strain of Newcastle disease virus (NDV) is protective against some strains but not universally effective due to antigenic differences. Additionally, viruses like Nipah (NiV) and Hendra (HeV) pose a high zoonotic risk, requiring vaccines that are effective in both animals and humans to prevent spillover, which is complicated by the variability of immune responses. Another challenge is achieving the right balance in the immune response; over-attenuated vaccines may not stimulate enough immunity, while under-attenuated vaccines can lead to adverse effects, as seen with respiratory syncytial virus (RSV) vaccines, which cause wheezing in infants.

Large-scale production of live-attenuated or inactivated viruses for vaccines remains difficult, especially in low-resource settings, necessitating efficient systems to meet global demand. Maternal antibodies can also interfere with vaccine efficacy in infants, making it crucial to develop vaccines that can overcome this barrier to ensure protection early in life. Furthermore, vaccine hesitancy has contributed to the resurgence of diseases like measles and mumps, highlighting the need for public education and transparent communication. The risk of reversion to virulence in live-attenuated vaccines, such as with NDV, also presents a concern, as outbreaks have occurred due to the vaccine strain reverting. In large-scale vaccination programs, like those for poultry, simultaneous vaccination can lead to interference, reducing the effectiveness of one or both vaccines.

Lastly, ensuring long-lasting immunity without causing excessive inflammation is a challenge, as some paramyxovirus vaccines, such as those for mumps or measles, may lose efficacy over time and require booster doses. Overcoming these challenges in efficacy, safety, production, and zoonotic transmission will require innovative approaches in vaccine design, production, and surveillance to provide broad, effective protection for both humans and animals.

6. Antiviral strategies for paramyxovirus infections

Despite the availability of vaccines for certain paramyxoviruses, antiviral therapy remains an important area of research due to the absence of effective treatments for many paramyxovirus infections. The high morbidity, particularly in immunocompromised individuals or populations lacking vaccination, emphasizes the need for effective antiviral treatments.

The paramyxovirus lifecycle begins when the virus binds to host cell receptors through its attachment.

(H) protein and subsequently fuses with the cell membrane *via* the F protein. Once inside, the viral RNA genome is released, and the virus hijacks the host's cellular machinery for replication. The newly formed viral proteins and RNA genomes are then packaged into new virions, which exit the host cell and spread the infection to other cells. This process is tightly regulated and presents several potential targets for antiviral intervention. The viral fusion process, replication machinery, and interactions with host immune responses are all critical components in the viral lifecycle that can be disrupted by antiviral therapies.

6.1 Antiviral approaches targeting the fusion (F) protein

The viral fusion (F) protein is a key player in paramyxovirus entry and is a major target for antiviral development. This protein undergoes conformational changes that allow the virus to fuse with the host cell membrane, facilitating infection. Inhibiting this process prevents viral entry and replication.

a. *Fusion-inhibitory peptides*: Fusion-inhibitory peptides are designed to bind to the F protein and block the conformational changes required for viral fusion. These peptides are effective in preventing viral entry into host cells [81]. Recent studies have shown that broad-spectrum fusion inhibitors targeting the paramyxovirus F protein can be effective against multiple paramyxovirus strains, including RSV, NDV, and measles [81, 82].

b. *Small-molecule inhibitors*: Small-molecule inhibitors targeting the F protein have emerged as an important therapeutic approach. These molecules are typically designed to interfere with the interaction between the viral F protein and the host cell membrane, preventing the fusion process. For example, inhibitors like palivizumab (used for RSV) and other experimental small molecules have shown promise in blocking viral fusion, thereby preventing infection [83–85].

6.2 Antiviral strategies targeting viral replication

After fusion and release of the viral genome, paramyxoviruses replicate their RNA genome inside the host cell. Inhibition of viral RNA polymerase or other enzymes involved in replication is another therapeutic strategy.

a. *RNA polymerase or replication complex inhibitors*: The polymerase complex, consisting of the L and P proteins, is essential for transcription and replication of viral RNA, making it a key target for antiviral therapies. Nucleoside analogs like favipiravir and ribavirin work by terminating RNA chains [86, 87], while non-nucleoside inhibitors disrupt the paramyxovirus RNA polymerase complex [88]. However, challenges such as resistance and host toxicity remain.

   Recent research has identified new antiviral agents targeting other viral proteins, such as the F and M proteins, which are crucial for viral fusion and assembly. For example, Nitazoxanide has shown broad-spectrum activity by interfering with the folding of these proteins [89].

b. *Host-targeted antiviral agents*: Another strategy is to target host cell proteins that paramyxoviruses rely on for replication. Host-targeted antiviral agents are designed to inhibit the activity of cellular factors that viruses manipulate to replicate their RNA genomes. Recent studies suggest that the host protein viperin, an enzyme involved in antiviral defense, can be targeted to inhibit paramyxovirus replication [90, 91].

6.3 Immune modulation and host immune response

One of the hallmarks of paramyxovirus infection is the ability to evade the host's immune response, particularly the innate immune system. Paramyxoviruses encode a variety of proteins that inhibit the host's interferon response and other immune defenses.

a. *Inhibition of immune evasion proteins*: The V protein of paramyxoviruses, such as measles virus (MV) and RSV, plays a critical role in immune evasion by blocking interferon production and disrupting the host's antiviral immune response [92]. Therapeutic strategies targeting these viral immune modulators, such as small molecules or monoclonal antibodies, have the potential to restore the immune system's ability to fight off the infection.

b. *Cytokine modulation*: Certain antiviral strategies focus on modulating the immune response to enhance host defenses [93]. For example, the use of immune adjuvants or cytokine therapies can boost the production of interferons and other cytokines, helping to restore the body's innate immune response against paramyxoviruses.

6.4 Challenges and future directions

Despite significant advances in antiviral drug development, there are several challenges in the treatment of paramyxovirus infections. One of the major challenges is the rapid mutation of viruses, which can lead to drug resistance. Another obstacle is the difficulty in delivering antiviral drugs effectively, particularly for respiratory infections like RSV, where delivery to the site of infection is crucial.

The development of broad-spectrum antiviral agents that target conserved viral mechanisms, such as the F protein, is a key focus of future research. Additionally, enhancing vaccine strategies and combining antiviral therapy with immunotherapies to modulate the host immune response may provide more effective treatments for paramyxovirus infections in the future. Ultimately, a multi-pronged approach involving antiviral drugs, vaccines, and immune therapies will be essential in combating the global threat posed by paramyxoviruses.

7. Conclusions

In conclusion, morbilliviruses, members of the Paramyxoviridae family, exhibit a complex interplay with host immune systems that facilitates their persistence and pathogenesis. Viral replication involves several key steps, including attachment to host cells *via* receptor interactions, fusion with the host cell membrane, and subsequent RNA replication and transcription within the cytoplasm. These processes culminate in virion assembly and release. The ability of morbilliviruses to evade immune responses, particularly through the suppression of type I interferon signaling and manipulation of immune cell function, complicates both therapeutic interventions and vaccine development. Despite advances in the development of vaccines and antiviral strategies, challenges such as immune evasion mechanisms, viral strain variability, and accessibility to treatments in resource-limited settings remain. Continued research into the molecular mechanisms underlying morbillivirus replication, immune modulation, and host-virus interactions is essential for the design of more effective vaccines and antiviral therapies. A multi-pronged approach, incorporating improved vaccines, antiviral agents, and immune modulatory treatments, is crucial for controlling morbillivirus infections and mitigating their impact on both human and veterinary populations.

Author details

Ashok Kumar[1], Ram Kumar[2], Anil Gattani[3*] and Sanju Mandal[4]

1 Animal Disease Research Centre, Guru Angad Dev Veterinary and Animal Sciences University, Ludhiana, Punjab, India

2 Department of Veterinary Microbiology, Rajasthan University of Veterinary and Animal Sciences, Bikaner, Rajasthan, India

3 Department of Veterinary Physiology and Biochemistry, Nanaji Deshmukh Veterinary Science University, Jabalpur, India

4 Department of Veterinary Physiology and Biochemistry, CoVSc and AH, The Nanaji Deshmukh Veterinary Science University, Jabalpur, India

*Address all correspondence to: gattanianil@gmail.com

IntechOpen

References

[1] Parija SC. Paramyxoviruses. In: Textbook of Microbiology and Immunology. Singapore: Springer Nature Singapore; 2023. pp. 811-824. DOI: 10.1007/978-981-19-3315-8_57

[2] Liu D. Classification of medically important viruses. In: Molecular Medical Microbiology. Academic Press; 2024. pp. 2061-2072. DOI: 10.1016/B978-0-12-818619-0.00161-1

[3] Fermin G. Virion structure, genome organization, and taxonomy of viruses. Viruses. 2018;**17**:17-54. DOI: 10.1016/B978-0-12-811257-1.00002-4

[4] De Vries RD, Duprex WP, De Swart RL. Morbillivirus infections: An introduction. Viruses. 2015;**7**(2):699-706. DOI: 10.3390/v7020699

[5] Dicker K, Järvelin AI, Garcia-Moreno M, Castello A. The importance of virion-incorporated cellular RNA-binding proteins in viral particle assembly and infectivity. In: Seminars in Cell and Developmental Biology. Vol. 111. Academic Press; 2021. pp. 108-118. DOI: 10.1016/j.semcdb.2020.08.002

[6] Dolnik O, Gerresheim GK, Biedenkopf N. New perspectives on the biogenesis of viral inclusion bodies in negative-sense RNA virus infections. Cells. 2021;**10**(6):1460. DOI: 10.3390/cells10061460

[7] Barrett T, Banyard AC, Diallo A. Molecular biology of the morbilliviruses. In: Rinderpest and peste des petits Ruminants. Academic Press; 2006. pp. 31-IV. DOI: 10.1016/B978-012088385-1/50033-2

[8] Kumar N, Maherchandani S, Kashyap SK, Singh SV, Sharma S, Chaubey KK, et al. Peste des petits ruminants virus infection of small ruminants: A comprehensive review. Viruses. 2014;**6**(6):2287-2327. DOI: 10.3390/v6062287

[9] Manjunath S, Kumar GR, Mishra BP, Mishra B, Sahoo AP, Joshi CG, et al. Genomic analysis of host–Peste des petits ruminants vaccine viral transcriptome uncovers transcription factors modulating immune regulatory pathways. Veterinary Research. 2015;**46**:1-15. DOI: 10.1186/s13567-015-0153-8

[10] Sourimant J, Plemper RK. Organization, function, and therapeutic targeting of the morbillivirus RNA-dependent RNA polymerase complex. Viruses. 2016;**8**(9):251. DOI: 10.3390/v8090251

[11] Vanmechelen B. Virus Discovery in Small Mammals: A Closer Look at the Families Arteriviridae and Paramyxoviridae. Faculty of Veterinary Medicine, Ghent University; 2022

[12] Pfaller CK, Cattaneo R, Schnell MJ. Reverse genetics of Mononegavirales: How they work, new vaccines, and new cancer therapeutics. Virology. 2015;**479**:331-344. DOI: 10.1016/j.virol.2015.01.029

[13] Yadav AK, Rajak KK, Bhatt M, Kumar A, Chakravarti S, Sankar M, et al. Comparative sequence analysis of morbillivirus receptors and its implication in host range expansion. Canadian Journal of Microbiology. 2019;**65**(11):783-794. DOI: 10.1139/cjm-2019-0008

[14] Gaur SK, Jain J, Chaudhary Y, Kaul R. Insights into the mechanism of Morbillivirus induced immune

suppression. Virology. 2024;**110212**:14-110212. DOI: 10.1016/j.virol.2024.110212

[15] Tatsuo H, Yanagi Y. The morbillivirus receptor SLAM (CD150). Microbiology and Immunology. 2002;**46**(3):135-142. DOI: 10.1111/j.1348-0421.2002.tb02678.x

[16] Von Messling V, Svitek N, Cattaneo R. Receptor (SLAM [CD150]) recognition and the V protein sustain swift lymphocyte-based invasion of mucosal tissue and lymphatic organs by a morbillivirus. Journal of Virology. 2006;**80**(12):6084-6092. DOI: 10.1128/jvi.00357-06

[17] Aversa G, Chang CC, Carballido JM, Cocks BG, de Vries JE. Engagement of the signaling lymphocytic activation molecule (SLAM) on activated T cells results in IL-2-independent, cyclosporin A-sensitive T cell proliferation and IFN-gamma production. Journal of Immunology (Baltimore, Md.: 1950). 1997;**158**(9):4036-4044

[18] Wu N, Veillette A. SLAM family receptors in normal immunity and immune pathologies. Current Opinion in Immunology. 2016;**38**:45-51. DOI: 10.1016/j.coi.2015.11.003

[19] Massé N, Ainouze M, Néel B, Wild TF, Buckland R, Langedijk JP. Measles virus (MV) hemagglutinin: Evidence that attachment sites for MV receptors SLAM and CD46 overlap on the globular head. Journal of Virology. 2004;**78**(17):9051-9063. DOI: 10.1128/JVI.78.17.9051-9063.2004

[20] Sato H, Yoneda M, Honda T, Kai C. Morbillivirus receptors and tropism: Multiple pathways for infection. Frontiers in Microbiology. 2012;**3**:75. DOI: 10.3389/fmicb.2012.00075

[21] Tatsuo H, Ono N, Yanagi Y. Morbilliviruses use signaling lymphocyte activation molecules (CD150) as cellular receptors. Journal of Virology. 2001;**75**(13):5842-5850. DOI: 10.1128/JVI.75.13.5842-5850.2001

[22] Adombi CM, Lelenta M, Lamien CE, Shamaki D, Koffi YM, Traoré A, et al. Monkey CV1 cell line expressing the sheep–goat SLAM protein: A highly sensitive cell line for the isolation of peste des petits ruminants virus from pathological specimens. Journal of Virological Methods. 2011;**173**(2):306-313. DOI: 10.1016/j.jviromet.2011.02.024

[23] Yanagi Y, Takeda M, Ohno S. Measles virus: Cellular receptors, tropism and pathogenesis. Journal of General Virus. 2006;**87**(10):2767-2779. DOI: 10.1099/vir.0.82221-0

[24] Leonard VH, Sinn PL, Hodge G, Miest T, Devaux P, Oezguen N, et al. Measles virus blind to its epithelial cell receptor remains virulent in rhesus monkeys but cannot cross the airway epithelium and is not shed. The Journal of Clinical Investigation. 2008;**118**(7):2448-2458. DOI: 10.1172/JCI35454

[25] Tahara M, Ito Y, Brindley MA, Ma X, He J, Xu S, et al. Functional and structural characterization of neutralizing epitopes of measles virus hemagglutinin protein. Journal of Virology. 2013;**87**(1):666-675. DOI: 10.1128/JVI.02033-12

[26] Pfeffermann K, Doerr M, Zirkel F, von Messling V. Morbillivirus pathogenesis and virus–host interactions. Advances in Virus Research. 2018;**100**:75-98. DOI: 10.1016/bs.aivir.2017.12.003

[27] Noyce RS, Richardson CD. Nectin 4 is the epithelial cell receptor for measles virus. Trends in Microbiology. 2012;**20**(9):429-439. DOI: 10.1016/j.tim.2012.05.006

[28] Mühlebach MD, Mateo M, Sinn PL, Prüfer S, Uhlig KM, Leonard VH, et al. Adherens junction protein nectin-4 is the epithelial receptor for measles virus. Nature. 2011;**480**(7378):530-533. DOI: 10.1038/nature10639

[29] Fujita K, Miura R, Yoneda M, Shimizu F, Sato H, Muto Y, et al. Host range and receptor utilization of canine distemper virus analyzed by recombinant viruses: Involvement of heparin-like molecule in CDV infection. Virology. 2007;**359**(2):324-335. DOI: 10.1016/j.virol.2006.09.018

[30] Yanagi Y, Ono N, Tatsuo H, Hashimoto K, Minagawa H. Measles virus receptor SLAM (CD150). Virology. 2002;**299**(2):155-161. DOI: 10.1006/viro.2002.1471

[31] Abdullah N, Kelly JT, Graham SC, Birch J, Gonçalves-Carneiro D, Mitchell T, et al. Structure-guided identification of a nonhuman morbillivirus with zoonotic potential. Journal of Virology. 2018;**92**(23):10-1128. DOI: 10.1128/JVI.01248-18

[32] Ader-Ebert N, Khosravi M, Herren M, Avila M, Alves L, Bringolf F, et al. Sequential conformational changes in the morbillivirus attachment protein initiate the membrane fusion process. PLoS Pathogens. 2015;**11**(5):e1004880. DOI: 10.1371/journal.ppat.1004880

[33] Navaratnarajah CK, Generous AR, Yousaf I, Cattaneo R. Receptor-mediated cell entry of paramyxoviruses: Mechanisms, and consequences for tropism and pathogenesis. The Journal of Biological Chemistry. 2020 Feb 28;**295**(9):2771-2786. Epub 2020 Jan 16. DOI: 10.1074/jbc.REV119.009961

[34] Kim CH, Kim CH. Viral protein interaction with host cells GSLs. Glycosphingolipids Signaling. 2020:53-92. DOI: 10.1007/978-981-15-5807-8_4

[35] Zinzula L, Beck F, Klumpe S, Bohn S, Pfeifer G, Bollschweiler D, et al. Cryo-EM structure of the cetacean morbillivirus nucleoprotein-RNA complex. Journal of Structural Biology. 2021;**213**(3):107750. DOI: 10.1016/j.jsb.2021.107750

[36] Munir M, Zohari S, Berg M, Munir M, Zohari S, Berg M. Genome organization of peste des petits ruminants virus. In: Molecular Biology and Pathogenesis of Peste Des Petits Ruminants Virus. 2013. pp. 1-22. DOI: 10.1007/978-3-642-31451-3_1

[37] Kozak M. Selection of initiation sites by eucaryotic ribosomes: Effect of inserting AUG triplets upstream from the coding sequence for preproinsulin. Nucleic Acids Research. 1984;**12**(9):3873-3893. DOI: 10.1093/nar/12.9.3873

[38] Schneider-Schaulies J. Cellular receptors for viruses: Links to tropism and pathogenesis. Journal of General Virology. 2000;**81**(6):1413-1429. DOI: 10.1099/0022-1317-81-6-1413

[39] Wertz GW, Perepelitsa VP, Ball LA. Gene rearrangement attenuates expression and lethality of a nonsegmented negative strand RNA virus. Proceedings of the National Academy of Sciences. 1998;**95**(7):3501-3506. DOI: 10.1073/pnas.95.7.3501

[40] Kolakofsky D, Le Mercier P, Iseni F, Garcin D. Viral RNA polymerase scanning and the gymnastics of Sendai virus RNA synthesis. Virology. 2004;**318**(2):463-473. DOI: 10.1016/j.virol.2003.10.031

[41] Maclachlan NJ, Dubovi EJ, editors. Fenner's Veterinary Virology. Academic Press; 2010

[42] Vincent S, Gerlier D, Manié SN. Measles virus assembly within membrane rafts. Journal of Virology. 2000;**74**(21):9911-9915. DOI: 10.1128/jvi.74.21.9911-9915.2000

[43] Laliberte JP, McGinnes LW, Morrison TG. Incorporation of functional HN-F glycoprotein-containing complexes into Newcastle disease virus is dependent on cholesterol and membrane lipid raft integrity. Journal of Virology. 2007;**81**(19):10636-10648. DOI: 10.1128/JVI.01119-07

[44] Pohl C, Duprex WP, Krohne G, Rima BK, Schneider-Schaulies S. Measles virus M and F proteins associate with detergent-resistant membrane fractions and promote formation of virus-like particles. Journal of General Virology. 2007;**88**(4):1243-1250. DOI: 10.1099/vir.0.82578-0

[45] El Najjar F, Schmitt AP, Dutch RE. Paramyxovirus glycoprotein incorporation, assembly and budding: A three way dance for infectious particle production. Viruses. 2014;**6**(8):3019-3054. DOI: 10.3390/v608301

[46] Rossman JS, Lamb RA. Viral membrane scission. Annual Review of Cell and Developmental Biology. 2013;**29**(1):551-569. DOI: 10.1146/annurev-cellbio-101011-155838

[47] Harrison MS, Sakaguchi T, Schmitt AP. Paramyxovirus assembly and budding: Building particles that transmit infections. The International Journal of Biochemistry and Cell Biology. 2010;**42**(9):1416-1429. DOI: 10.1016/j.biocel.2010.04.005

[48] Takimoto T, Portner A. Molecular mechanism of paramyxovirus budding. Virus Research. 2004;**106**(2):133-145

[49] Duan Z, Hu Z, Zhu J, Xu H, Chen J, Liu H, et al. Mutations in the FPIV motif of Newcastle disease virus matrix protein attenuate virus replication and reduce virus budding. Archives of Virology. 2014;**159**:1813-1819. DOI: 10.1007/s00705-014-1998-2

[50] Salditt A, Koethe S, Pohl C, Harms H, Kolesnikova L, Becker S, et al. Measles virus M protein-driven particle production does not involve the endosomal sorting complex required for transport (ESCRT) system. Journal of General Virology. 2010;**91**(6):1464-1472. DOI: 10.1099/vir.0.018523-0

[51] Fouillot-Coriou N, Roux L. Structure–function analysis of the Sendai virus F and HN cytoplasmic domain: Different role for the two proteins in the production of virus particle. Virology. 2000;**270**(2):464-475. DOI: 10.1006/viro.2000.0291

[52] Essaidi-Laziosi M, Shevtsova A, Gerlier D, Roux L. Mutation of the TYTLE motif in the cytoplasmic tail of the Sendai virus fusion protein deeply affects viral assembly and particle production. PLoS One. 2013;**8**(12):e78074. DOI: 10.1371/journal.pone.0078074

[53] Liljeroos L, Krzyzaniak MA, Helenius A, Butcher SJ. Architecture of respiratory syncytial virus revealed by electron cryotomography. Proceedings of the National Academy of Sciences. 2013;**110**(27):11133-11138. DOI: 10.1073/pnas.1309070110

[54] Gonçalves Carneiro VD. Molecular Mechanisms of Measles Virus Entry and Exit (Doctoral Dissertation, University of Birmingham). 2017. Available from: http://etheses.bham.ac.uk/id/eprint/7514

[55] Naim HY, Ehler E, Billeter MA. Measles virus matrix protein specifies apical virus release and glycoprotein

sorting in epithelial cells. The EMBO Journal. 2000;**19**(14):3576-3585. DOI: 10.1093/emboj/19.14.3576

[56] Parks GD, Alexander-Miller MA. Paramyxovirus activation and inhibition of innate immune responses. Journal of Molecular Biology. 2013;**425**(24):4872-4892. DOI: 10.1016/j.jmb.2013.09.015

[57] Siering O, Cattaneo R, Pfaller CK. C proteins: Controllers of orderly paramyxovirus replication and of the innate immune response. Viruses. 2022;**14**(1):137. DOI: 10.3390/v14010137

[58] Childs K, Andrejeva J, Randall RE, Goodbourn S. Mechanism of mda-5 inhibition by paramyxovirus V proteins. Journal of Virology. 2009;**83**(3):1465-1473. DOI: 10.1128/JVI.01768-08

[59] Devasthanam AS. Mechanisms underlying the inhibition of interferon signaling by viruses. Virulence. 2014;**5**(2):270-277. DOI: 10.4161/viru.27902

[60] Ramachandran A, Horvath CM. Dissociation of paramyxovirus interferon evasion activities: Universal and virus-specific requirements for conserved V protein amino acids in MDA5 interference. Journal of Virology. 2010;**84**(21):11152-11163. DOI: 10.1128/JVI.01375-10

[61] Andrejeva J, Young D, Goodbourn S, Randall RE. Degradation of STAT1 and STAT2 by the V proteins of simian virus 5 and human parainfluenza virus type 2, respectively: Consequences for virus replication in the presence of alpha/beta and gamma interferons. Journal of Virology. 2002;**76**(5):2159-2167. DOI: 10.1128/jvi.76.5.2159-2167.2002

[62] Ma X, Yang X, Nian X, Zhang Z, Dou Y, Zhang X, et al. Identification of amino-acid residues in the V protein of peste des petits ruminants essential for interference and suppression of STAT-mediated interferon signaling. Virology. 2015;**483**:54-63. DOI: 10.1016/j.virol.2015.03.039

[63] Röthlisberger A, Wiener D, Schweizer M, Peterhans E, Zurbriggen A, Plattet P. Two domains of the V protein of virulent canine distemper virus selectively inhibit STAT1 and STAT2 nuclear import. Journal of Virology. 2010;**84**(13):6328-6343. DOI: 10.1128/JVI.01878-09

[64] Agrawal P, Nawadkar R, Ojha H, Kumar J, Sahu A. Complement evasion strategies of viruses: An overview. Frontiers in Microbiology. 2017;**8**:1117. DOI: 10.3389/fmicb.2017.01117

[65] Ng SSM, Li A, Pavlakis GN, Ozato K, Kino T. Viral infection increases glucocorticoid-induced interleukin-10 production through ERK-mediated phosphorylation of the glucocorticoid receptor in dendritic cells: Potential clinical implications. PLoS One. 2013;**8**(5):e63587. DOI: 10.1371/journal.pone.0063587

[66] Schneider-Schaulies J, Schneider-Schaulies S. Receptor interactions, tropism, and mechanisms involved in morbillivirus-induced immunomodulation. Advances in Virus Research. 2008;**71**:173-205. DOI: 10.1016/S0065-3527(08)00004-3

[67] Gupta MR, Kolli D, Molteni C, Casola A, Garofalo RP. Paramyxovirus infection regulates T cell responses by BDCA-1+ and BDCA-3+ myeloid dendritic cells. PLoS One. 2014;**9**(6):e99227. DOI: 10.1371/journal.pone.0099227

[68] Rijks JM, Osterhaus A, Kuiken T, Frölich K. Morbillivirus Infections. Wiley Online Library; 2012. p. 99. DOI: 10.1002/9781118342442

[69] Marcink TC, Zipursky G, Sobolik EB, Golub K, Herman E, Stearns K, et al. How a paramyxovirus fusion/entry complex adapts to escape a neutralizing antibody. Nature Communications. 2024;**15**(1):8831. DOI: 10.1038/s41467-024-53082-y

[70] Banoun H. Measles and antibody-dependent enhancement (ADE): History and mechanisms. In: Exploratory Research and Hypothesis in Medicine. 2022. pp. 000-000. DOI: 10.14218/ERHM.2022.00018

[71] Kulkarni R. Antibody-dependent enhancement of viral infections. In: Dynamics of Immune Activation in Viral Diseases. 2020. pp. 9-41. DOI: 10.1007/978-981-15-1045-8_2

[72] Porterfield JS. Antibody-dependent enhancement of viral infectivity. Advances in Virus Research. 1986;**31**:335-355. DOI: 10.1016/s0065-3527(08)60268-7

[73] Kumar N, Barua S, Riyesh T, Tripathi BN. Advances in peste des petits ruminants vaccines. Veterinary Microbiology. 2017;**206**:91-101. DOI: 10.1016/j.vetmic.2017.01.010

[74] Bala N. Studies on Thermostable Newcastle Disease Virus Induced Cytokine Expression in Chicken Embryo Fibroblastt. Hisar, India: University of Veterinary and Animal Sciences; 2023

[75] Dimitrov KM, Afonso CL, Yu Q, Miller PJ. Newcastle disease vaccines—A solved problem or a continuous challenge? Veterinary Microbiology. 2017;**206**:126-136. DOI: 10.1016/j.vetmic.2016.12.019

[76] Fulber JP, Kamen AA. Development and scalable production of Newcastle disease virus-vectored vaccines for human and veterinary use. Viruses. 2022;**14**(5):975. DOI: 10.3390/v14050975

[77] Martella V, Blixenkrone-Møller M, Elia G, Lucente MS, Cirone F, Decaro N, et al. Lights and shades on an historical vaccine canine distemper virus, the Rockborn strain. Vaccine. 2011;**29**(6):1222-1227. DOI: 10.1016/j.vaccine.2010.12.001

[78] August A, Shaw CA, Lee H, Knightly C, Kalidindia S, Chu L, et al. Safety and immunogenicity of an mRNA-based human metapneumovirus and parainfluenza virus type 3 combined vaccine in healthy adults. Paper Presented at the Open Forum Infectious Diseases. 2022;7(9):ofac206. DOI: 10.1093/ofid/ofac206

[79] Hurwitz JL. Respiratory syncytial virus vaccine development. Expert Review of Vaccines. 2011;**10**(10):1415-1433. DOI: 10.1586/erv.11.120

[80] McEachern JA, Bingham J, Crameri G, Green DJ, Hancock TJ, Middleton D, et al. A recombinant subunit vaccine formulation protects against lethal Nipah virus challenge in cats. Vaccine. 2008;**26**(31):3842-3852. DOI: 10.1016/j.vaccine.2008.05.016

[81] Düzgüneş N, Fernandez-Fuentes N, Konopka K. Inhibition of viral membrane fusion by peptides and approaches to peptide design. Pathogens. 2021;**10**(12):1599. DOI: 10.3390/pathogens10121599

[82] Monteiro A, Yu KO, Hicar MD. Peptide-based fusion inhibitors for preventing the six-helix bundle formation of class I fusion proteins: HIV and beyond. Current HIV Research. 2021;**19**(6):465-475. DOI: 10.2174/1570162X19666210908115231

[83] Battles MB, Langedijk JP, Furmanova-Hollenstein P, Chaiwatpongsakorn S, Costello HM, Kwanten L, et al. Molecular mechanism

of respiratory syncytial virus fusion inhibitors. Nature Chemical Biology. 2016;**12**(2):87-93. DOI: 10.1038/nchembio.1982

[84] Elawar F, Oraby AK, Kieser Q, Jensen LD, Culp T, West FG, et al. Pharmacological targets and emerging treatments for respiratory syncytial virus bronchiolitis. Pharmacology and Therapeutics. 2021;**220**:107712. DOI: 10.1016/j.pharmthera.2020.107712

[85] Felicetti T, Sarnari C, Gaito R, Tabarrini O, Manfroni G. Recent progress toward the discovery of small molecules as novel anti-respiratory syncytial virus agents. Journal of Medicinal Chemistry. 2024;**67**(14):11543-11579. DOI: 10.1021/acs.jmedchem.4c00630

[86] Jochmans D, van Nieuwkoop S, Smits S, Neyts J, Fouchier R, Van Den Hoogen B. Antiviral activity of favipiravir (T-705) against a broad range of paramyxoviruses in vitro and against human metapneumovirus in hamsters. Antimicrobial Agents and Chemotherapy. 2016;**60**(8):4620-4629. DOI: 10.1128/AAC.00709-16

[87] Smyk JM, Majewska A. Favipiravir in the battle with respiratory viruses. Mini Reviews in Medicinal Chemistry. 2022;**22**(17):2224-2236. DOI: 10.2174/1389557522666220218122744

[88] Cox R, Plemper RK. The paramyxovirus polymerase complex as a target for next-generation anti-paramyxovirus therapeutics. Frontiers in Microbiology. 2015;**6**:459. DOI: 10.3389/fmicb.2015.00459

[89] Piacentini S, La Frazia S, Riccio A, Pedersen JZ, Topai A, Nicolotti O, et al. Nitazoxanide inhibits paramyxovirus replication by targeting the fusion protein folding: Role of glycoprotein-specific thiol oxidoreductase ERp57. Scientific Reports. 2018;**8**(1):10425. DOI: 10.1038/s41598-018-28172-9

[90] Farrukee R, Ait-Goughoulte M, Saunders PM, Londrigan SL, Reading PC. Host cell restriction factors of paramyxoviruses and pneumoviruses. Viruses. 2020;**12**(12):1381. DOI: 10.3390/v12121381

[91] Freed EO, Gale M Jr. Antiviral innate immunity: Editorial overview. Journal of Molecular Biology. 2014;**426**(6):1129. DOI: 10.1016/j.jmb.2014.01.005

[92] Wang C, Wang T, Duan L, Chen H, Hu R, Wang X, et al. Evasion of host antiviral innate immunity by paramyxovirus accessory proteins. Frontiers in Microbiology. 2022;**12**:790191. DOI: 10.3389/fmicb.2021.790191

[93] Bhol NK, Bhanjadeo MM, Singh AK, Dash UC, Ojha RR, Majhi S, et al. The interplay between cytokines, inflammation, and antioxidants: Mechanistic insights and therapeutic potentials of various antioxidants and anti-cytokine compounds. Biomedicine and Pharmacotherapy. 2024;**178**:117177. DOI: 10.1016/j.biopha.2024.117177