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TOPIC HIGHLIGHT

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Paramyxovirus evasion of innate immunity: Diverse strategies for common targets

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Abstract

The paramyxoviruses are a family of > 30 viruses that variously infect humans, other mammals and fish to cause diverse outcomes, ranging from asymptomatic to lethal disease, with the zoonotic paramyxoviruses Nipah and Hendra showing up to 70% case-fatality rate in humans. The capacity to evade host immunity is central to viral infection, and paramyxoviruses have evolved multiple strategies to overcome the host interferon (IFN)-mediated innate immune response through the activity of their IFN-antagonist proteins. Although paramyxovirus IFN antagonists generally target common factors of the IFN system, including melanoma differentiation associated factor 5, retinoic acid-inducible gene-I, signal transducers and activators of transcription (STAT)1 and STAT2, and IFN regulatory factor 3, the mechanisms of antagonism show remarkable diversity between different genera and even individual members of the same genus; the reasons for this diversity, however, are not currently understood. Here, we review the IFN antagonism strategies of paramyxoviruses, highlighting mechanistic differences observed between individual species and genera. We also discuss potential sources of this diversity, including biological differences in the host and/or tissue specificity of different paramyxoviruses, and potential effects of experimental approaches that have largely relied on *in vitro* systems. Importantly, recent studies using recombinant virus systems and animal infection models are beginning to clarify the importance of certain mechanisms of IFN antagonism to *in vivo* infections, providing important indications not only of their critical importance to virulence, but also of their potential targeting for new therapeutic/vaccine approaches.

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Key words: Paramyxoviridae; Innate immunity; Signal transducers and activators of transcription 1; Signal transducers and activators of transcription 2; Melanoma differentiation associated factor 5; Retinoic acid-inducible gene-I

Core tip: The paramyxoviruses are a family of > 30 viruses that variously infect humans, other mammals and fish to cause diverse outcomes, ranging from asymptomatic to lethal disease, with the zoonotic paramyxoviruses Nipah and Hendra showing up to 70% case-fatality rate in humans. Here, we review the interferon antagonism strategies of paramyxoviruses, highlighting mechanistic differences observed between individual species and genera. We also discuss potential sources of this diversity, including biological differences in the host and/or tissue specificity of different paramyxoviruses, and potential effects of experimental approaches that have largely relied on *in vitro* systems.

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INTRODUCTION

Since the discovery more than 50 years ago of type I

interferons (IFNs) as the principal mediators of mammalian innate antiviral responses, it has become increasingly evident that infection by viruses depends on the capacity to counteract host cell IFN responses. Viruses have evolved diverse strategies to antagonise IFN responses, often by hijacking and modifying cellular regulatory pathways through the activity of specific viral IFN-antagonist proteins. Among the best-studied viruses in this respect are the paramyxoviruses, which include established human pathogens such as measles virus (MeV) and mumps virus (MuV), and emerging zoonotic viruses such as the henipaviruses Nipah virus (NiV) and Hendra virus (HeV). Although effective vaccines are available for MeV, it remains a leading cause of fatalities in children, with almost 140000 human deaths globally in 2010[1], while the henipaviruses show remarkable pathogenicity, with case-fatality rates between 40%-70% in humans[2-5].

The paramyxoviruses are a subfamily of the *Paramyxoviridae* family [order *Mononegavirales* (MNV)] of enveloped, non-segmented negative-strand RNA viruses (NNSV), which also includes the *Pneumovirus* subfamily[6,7]. Based largely on antigenic cross-reactivity and neuramidase activity paramyxoviruses are currently classified into seven genera[6,7]: *Rubulavirus*, *Avulavirus*, *Henipavirus*, *Morbillivirus*, *Respirovirus, Ferlavirus* and *Aquaparamyxovirus* (Table 1). Members of the paramyxovirus family show diverse tissue tropism and infect a variety of species in a fashion that does not appear to be specific to genus classification (Table 1). Because their relatively small genomes lack dedicated IFN-antagonist genes, paramyxoviruses generally encode IFN-antagonists as accessory protein isoforms encoded within their conserved P genes, another factor in genus classification[6]. These IFN antagonists broadly target several members of a select group of signalling molecules of the IFN system, including melanoma differentiation associated factor 5 (MDA5), retinoic acid-inducible gene- I (RIG)- I , IFN regulatory factor (IRF)-3, and signal transducers and activators of transcription (STAT)1 and STAT2, but use diverse mechanisms including proteosomal degradation, inhibition of phosphorylation, and subcellular mis-localisation. Intriguingly, the mechanisms can vary significantly between different genera and, in some cases, different species of the same genera.

Here we review the mechanistic data relating to paramyxovirus IFN antagonism with a focus on common and distinct features within the family, before discussing possible origins of the diversity within the family. Although much of the available research on paramyxovirus IFN antagonism has been restricted to *in vitro* studies, recent findings using *in vivo* infection and recombinant virus systems point to a pivotal role in pathogenicity that may provide potent targets for the development of new vaccines/antiviral therapeutics.

PARAMYXOVIRUS P GENE

While viruses with large genomes can encode dedicated IFN-antagonist proteins, the high error rates of the RNA-dependent RNA polymerase means that RNA viruses generally have restricted genome sizes, with the paramyxovirus genome containing only six principal genes to express essential structural/replication factors, specifically M (matrix), G/HN/H (attachment), F (fusion), L (polymerase), N/NP (nucleocapsid) and P (phosphoprotein) (Figure 1A). Thus the IFN-antagonists of RNA viruses are often encoded as "accessory" protein isoforms within one or more of the conserved genes[8,9]; in paramyxoviruses up to 9 proteins are encoded in the P gene, including V, C, and P proteins and a protein variously named W, D or I, which have established IFN antagonist functions.

Isoform expression from the *paramyxovirus P* gene is variously achieved by a conserved RNA-editing mechanism, and through the use of internal start codons and alternate open reading frames (ORFs). RNA editing is mediated by the viral RNA-dependent RNA polymerase

Table 1 Genus classification and major host species of the Paramyxovirinae subfamily

Genus	Virus	Major host
Morbillivirus	Measles virus[1]	Human
	Canine distemper virus	Canine
	Rinderpest virus	Bovine
	Peste-des-petits-ruminants virus	Caprine
	Phocine distemper virus	Phocine
	Cetacean morbillivirus	Cetacean
Rubulavirus	Mumps virus[1]	Human
	Parainfluenza virus 5 (previously, Simian virus 5)	Human
	Human parainfluenza virus 2, 4a and 4b	Human
	Mapuera virus	Chiropteran[2]
	Porcine rubulavirus	Porcine
Respirovirus	Sendai virus[1]	Murine
	Human parainfluenza virus 1, 3	Human
	Bovine parainfluenza virus 3	Bovine
Avulavirus	Newcastle disease virus[1]	Avian
	Avian paramyxoviruses 2-9	Avian
Henipavirus	Hendra virus[1]	Chiropteran/ equine /human[3]
	Nipah virus	Chiropteran/ porcine/ human[3]
	Cedar virus	Chiropteran[2]
Aquaparamyxovirus	Atlantic salmon paramyxovirus[1]	Piscine
Ferlavirus	Fer-de-Lance virus[1]	Serpentine
Unassigned	J-virus	Murine
	Beilong virus	Murine
	Tailam virus	Murine
	Menangle virus	Porcine
	Tioman virus	Chiropteran[2]
	Tupaia virus	Chiropteran[2]
	Salem virus	Chiropteran[2]
	Mossman virus	Chiropteran[2]
	Nariva virus	Chiropteran[2]
	Pigeon paramyxovirus 1	Avian

[1]Type species for each genus; [2]Virus isolated from chiropteran hosts, but pathology and broader host range is unknown; [3]Virus is highly pathogenic in humans, but humans are not a major host.

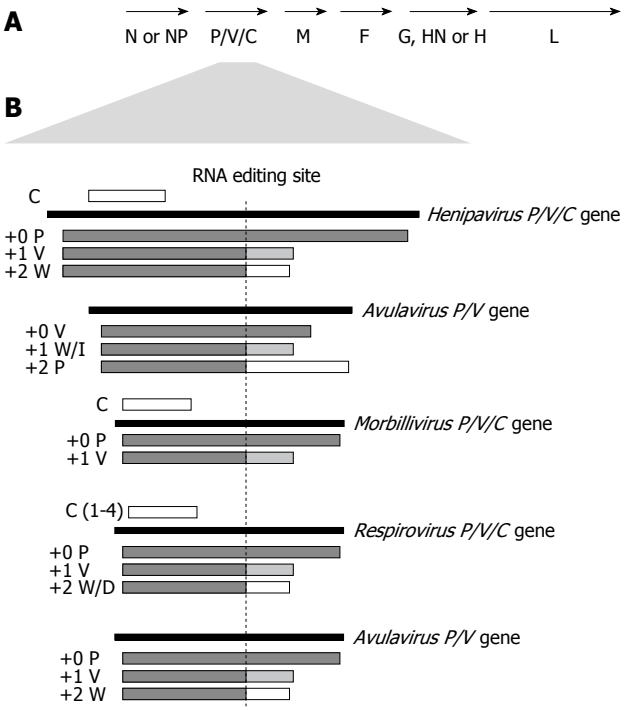

Figure 1 Coding strategies of *paramyxovirus P* genes. A: Genome organisation of the *Paramyxovirinae* subfamily; B: Paramyxoviruses express multiple proteins from the P gene through RNA editing to insert additional non-coded G nucleotides into P gene transcripts at the editing site (indicated), causing a frameshift in the downstream open reading frame (ORF) to generate distinct C-termini. Editing strategies of the 5 best-studied genera are shown, with proteins produced from unedited (+0), or edited (+1 or +2 frameshift) mRNA indicated below the P gene. Several members of the henipavirus, respirovirus and morbillivirus genera, but not the rubulaviruses or avulaviruses, produce one or more C proteins by translation from internal start codon(s) in alternate ORF(s) (indicated as a white bar above the P gene).

through the insertion of additional non-coded guanosine (G) nucleotides into P gene mRNA transcripts at a predetermined purine rich editing site. This causes a +1 or +2 frameshift in the downstream ORF[10-12] which results in the generation of two or three distinct proteins (P, V and W/D/I), which have common N-terminal sequences but unique C-termini (Figure 1B). A comparable editing process is used by Ebolavirus of the *Filovirus* family to produce isoforms from its G gene[13]. This mechanism is conserved among all paramyxoviruses examined except human parainfluenza virus (hPIV) 1 and the recently discovered cedar virus[14,15].

P protein, the polymerase cofactor essential to genome transcription/replication processes, is usually generated from the unedited ORF as the principal P gene product, with the production of edited RNA varying in a broadly genus-specific fashion (Figure 1B), although the +1 frameshift commonly encodes V protein and the +2 frameshift W/D/I[16,17]. Members of the *Rubulavirus* genus uniquely encode V protein in the unedited transcript, with P protein expression requiring editing (Figure 1B)[9], with c. 63% of the P gene mRNA transcribed unedited by the rubulavirus MuV, indicative of a particular requirement for high levels of V protein by these viruses[9]. The henipaviruses have the highest editing frequency of the paramyxoviruses: 66% to 94% of transcripts are edited, compared with c. 42% for MeV (*Morbillivirus* genus), and c. 31% for Sendai virus (SeV) (*Respirovirus* genus)[18-21]. Henipaviruses insert up to 11 additional G nucleotides[18], and in NiV-infected cells P transcripts are detected at the highest levels (c. 60%-100%) early in infection, with V and W transcripts peaking between 9.5-24 h post-infection (up to 59% and 37% respectively). This suggests that editing is regulated to enable particularly important roles for V and W late in infection[18], although other factors such as mRNA/protein stability are likely to affect the final levels of protein.

Henipaviruses, morbilliviruses, and respiroviruses use a start codon within the P gene in an alternate ORF to produce a C protein (Figure 1B), while the SeV P gene encodes up to five proteins other than P, V and W: four C proteins encoded by overlapping sequences in the +1 reading frame, and X protein, a truncated version of P protein translated from an internal start site[11,22,23]. HeV, but not NiV, encodes a putative SB (short basic) protein, homologous to SB of several viruses of other MNV families[21]. These differences in P gene coding capacity indicate different requirements of specific viruses for accessory proteins, possibly due to host/tissue specific aspects of IFN signalling (see below).

The V proteins are generally considered the principal IFN-antagonists of paramyxoviruses, and are the best studied of the P gene accessory proteins. However, there is increasing evidence that P, W, or C proteins of paramyxoviruses including NiV, MeV, and SeV play important roles in IFN antagonism by distinct mechanisms. Thus, it seems that most if not all P gene accessory proteins have evolved for roles in immune evasion as important pathogenicity factors[24-28]. Consistent with important roles in infection, V proteins show high conservation in the unique C-terminal region (Figure 2)[29-31], including absolute conservation of seven conserved cysteine residues and a histidine, which form a zinc-finger domain (highlighted in Figure 2). In the parainfluenza virus 5 (PIV5) V protein (*Rubulavirus* genus), two zinc atoms are coordinated by two loops, incorporating V residues H171, C190, C215, C218, and C194, C206, C208, C211 respectively[31,32], and mutations of these residues disrupt certain IFN inhibitory functions (see below), although the role of zinc-binding is not known. The C-terminal region is also important to the formation of oligomeric structures of V proteins and certain innate immune factors important to IFN antagonism[33].

TYPE I IFN SYSTEM

Mammalian cell responses to infection depend on the detection of pathogen-associated molecular patterns (PAMPs) produced during microbial infection and replication, such as single-stranded RNA (ssRNA), double-stranded RNA (dsRNA) and RNA with exposed/uncapped 5' triphosphates that are generated by RNA viruses[34,35]. Detection of virus components is principally

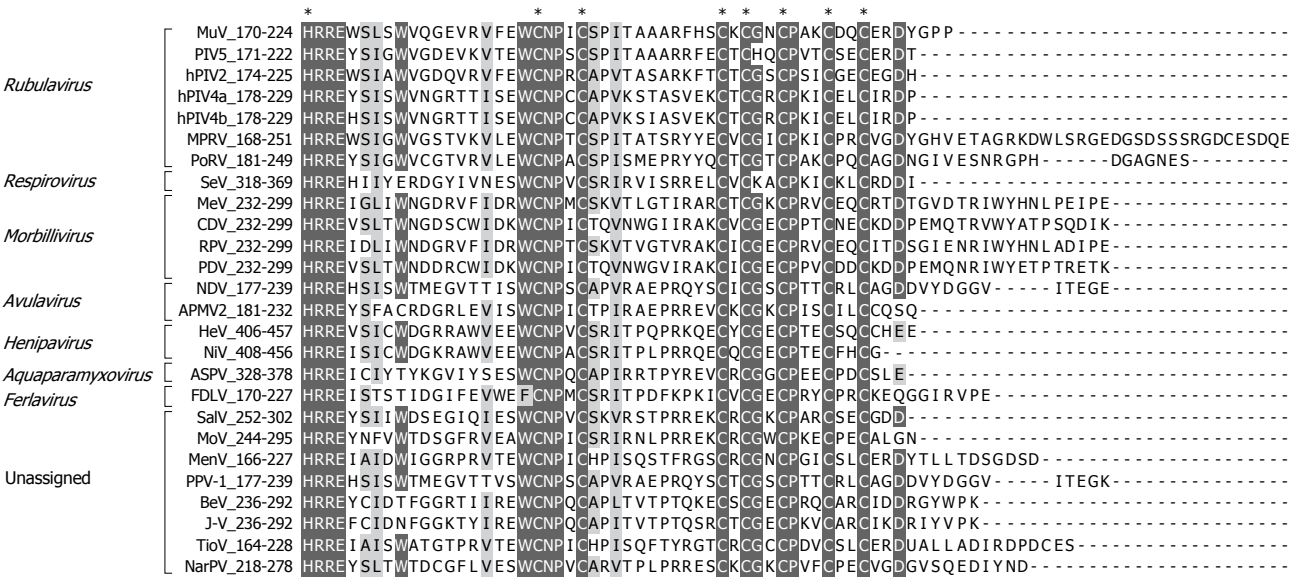

Figure 2 Conserved residues in the paramyxovirus V C-terminal domain. Paramyxovirus V protein C-terminal sequences are aligned with identical and similar residues highlighted. Asterisks indicate absolutely conserved histidine and cysteine residues involved in zinc-binding (see text for details). Residue numbers are indicated in the sequence titles. MuV: Mumps virus; PIV5: Parainfluenza virus 5; hPIV: Human PIV; MPRV: Mapuera virus; PoRV: Porcine rubulavirus; SeV: Sendai virus; MeV: Measles virus; CDV: Canine distemper virus; RPV: Rinderpest virus; PDV: Phocine distemper virus; NDV: Newcastle disease virus; APMV2: Avian paramyxovirus 2; HeV: Hendra virus; NiV: Nipah virus; ASPV: Atlantic Salmon Paramyxovirus; FDLV: Fer-de-Lance virus; SalV: Salem virus; MoV: Mossman virus; MenV: Menangle virus; PPV-1: Pigeon paramyxovirus 1; BeV: Beilong virus; J-V: J-virus; TioV: Tioman virus; NarPV: Nariva virus.

mediated by three types of PAMP-recognition-receptors (PRRs): Toll-like receptors (TLRs) and RIG- I -like receptors (RLRs), thought to be the main receptors responsible for type I IFN (IFNα/β) induction, and nucleotide-oligomerisation domain-like receptors[36].

TLRs are trans-membrane proteins expressed at the plasma membrane or on intracellular structures such as endosomes and the endoplasmic reticulum[37,38] to detect extracellular viral nucleic acids such as dsRNA (TLR3)[37-40] and G/U-rich ssRNAs (TLR7)[38]. By contrast, the almost ubiquitously expressed RLR helicases RIG- I and MDA5 detect viral dsRNA in the cytoplasm of infected cells[36,41-47]; RIG- I also recognises cytoplasmic 5' tri-phosphorylated and uncapped viral ssRNA[48-50]. RNA-activated MDA5 and RIG- I interact with the mitochondrial membrane-associated adaptor protein IFNβ promoter stimulator 1 (IPS-1, also known as MAVS, VISA, or CARDIF) *via* their caspase activation and recruitment domains (CARDs) to trigger downstream signalling (Figure 3). TLRs activate distinct pathways (Figure 3), but RLR and TLR signalling converges with the phosphorylation of the constitutively expressed cytoplasmic transcription factors IRF-3, as well as nuclear factor κB (NF-κB), causing their translocation into the nucleus to activate the transcription of early type I IFNs (IFNβ and IFNα4)[36,51-56]. Most human cell types can produce type I IFNs in response to infection, with "professional" IFN-producing immune cells including plasmacytoid DCs and macrophages being major producers during infection, due to constitutive expression of IRF-7 (which requires induction in other cell types) and the use of alternative TLR-9 pathways[57]. Importantly, paramyxoviruses can induce type I IFN expression through RIG- I , MDA5 and TLR pathways (Figure 3)[42,58,59].

Type I IFNs signal in autocrine and paracrine fashion, binding to the ubiquitously expressed IFNα/β receptor (IFNAR) to activate the Janus kinase (JAK)/STAT signalling pathway (Figure 4), resulting in the phosphorylation and nuclear translocation of STAT1 and STAT2 proteins. In the form of a heterotrimeric complex [IFN-stimulated gene factor 3 (ISGF3)] which incorporates IRF-9, STAT1 and STAT2 trans-activate hundreds of IFN-stimulated genes, many of which encode known antiviral proteins including protein kinase R, which inhibits translation of mRNAs[60]; 2'5'-oligoadenylate synthetase, which activates RNase L to effect degradation of ssRNA[60]; Mx GTPase proteins that interfere with the growth of certain viruses including the paramyxoviruses[52]; and PML, which has antiviral properties but with unresolved mechanisms[52]. IRF-7 is also up regulated to activate a positive feedback loop by forming heterodimers with IRF-3 (Figure 3) inducing "late" IFNα subtypes for prolonged responses to infection[61].

Although signalling through STAT1/2 heterodimers is essential to type I IFN responses, type I IFN activates other complexes including homodimers of STAT1 and STAT3 and STAT1-STAT3 heterodimers, which have different gene specificity or regulatory roles[62], and recent data suggest that STAT2 can also effect STAT1-independent antiviral functions[63]. Thus, type I IFN activation can affect diverse gene expression through distinct pathways. STATs are also critical to signalling by type Ⅱ and Ⅲ IFNs and various other cytokines[54,64] such as interleukin (IL)-6[65,66], presenting potential targets for viral inhibition of several immune signalling systems.

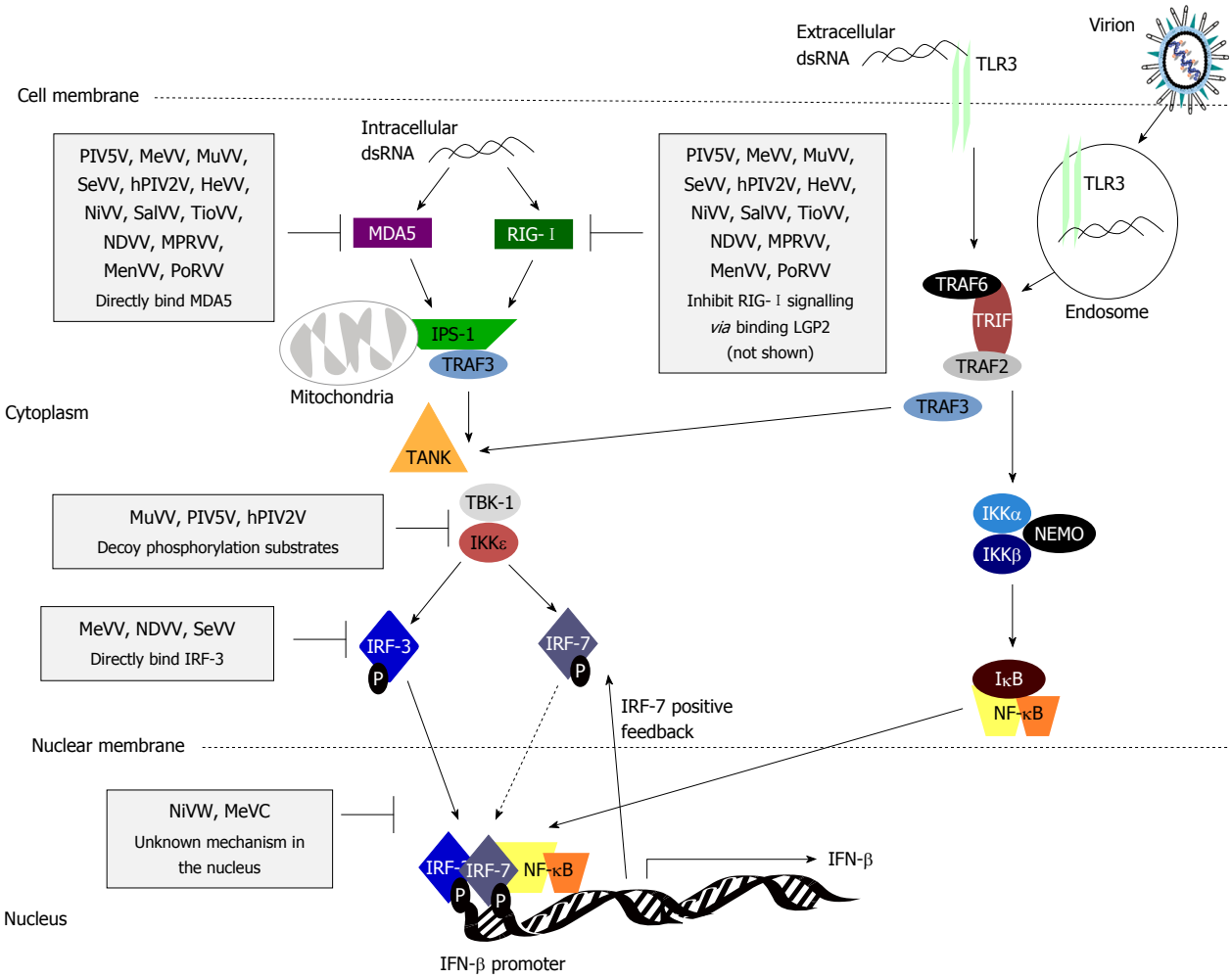

Figure 3 Type I interferon induction is inhibited by paramyxovirus interferon-antagonist proteins at multiple stages. Pathogen-associated molecular patterns (PAMPs) generated during virus infection, such as dsRNA, are recognised by PRRs including endosomal/surface expressed Toll-like receptor 3 (TLR3) and cytoplasmic retinoic acid-inducible gene- I (RIG- I)/melanoma differentiation associated protein 5 (MDA5). TLR3 signals through the adaptor molecule Toll/interleukin-1 receptor domain-containing adaptor inducing interferon (IFN)β (TRIF), which recruits tumor necrosis factor receptor-associated factor (TRAF)2 to activate the inhibitor of nuclear factor κB (NF-κB) kinase (IKK)α/β kinases to phosphorylate inhibitory inhibitor of NF-κB (IκB), triggering its degradation and activation/nuclear translocation of NF-κB. TLR3 signalling *via* TRAF3 results in phosphorylation/activation of IFN regulatory factor (IRF)-3, causing its homodimerisation, or heterodimerisation with IRF-7 in professional IFN producing/IFN-primed cells, and translocation into the nucleus where, with NF-κB and activating transcription factor 2 (ATF2)/c-jun (not shown), it activates early type I IFN transcription. RIG- I and MDA5 also induce phosphorylation of IRF-3 following recognition of cytoplasmic PAMPs in infected cells *via* interaction with the mitochondrial membrane protein IFNβ promoter stimulator 1 (IPS-1), which recruits and activates TANK and the TANK-binding kinases (TBKs). TBK-1 and IKKε *via* the E3 ubiquitin ligase TRAF3. Many paramyxoviruses target this pathway; steps commonly targeted are indicated (black bars) with specific examples of the paramyxovirus proteins responsible (see text for details). DC: Dendritic cell; PIV5: Parainfluenza virus 5; MeV: Measles virus; MuV: Mumps virus; SeV: Sendai virus; hPIV: Human PIV; HeV: Hendra virus; NiV: Nipah virus; SalV: Salem virus; TioV: Tioman virus; NDV: Newcastle disease virus; MPRV: Mapuera virus; MenV: Menangle virus; PoRV: Porcine rubulavirus; LGP2: Laboratory of genetics and physiology 2.

CELLULAR TARGETS OF PARAMYXOVIRUS IFN ANTAGONISTS

A large body of evidence indicates that viruses/IFN-antagonist proteins generally target multiple steps in the IFN system[52,67,68]. The requirement for this broad targeting probably relates to factors such as differences in the kinetics of viral IFN-antagonist expression compared with the mounting of IFN responses, the contribution of infected cells and non-infected professional IFN producing cells, and the overall antiviral potency of the IFN system. Most paramyxoviruses can inhibit both IFN induction and signalling by targeting several cellular proteins. Intriguingly, although paramyxoviruses generally target common factors including MDA5, IRF-3 and STATs, the mechanisms of inhibition show significant divergence between different viruses.

Targeting of MDA5

The V proteins of at least 13 paramyxoviruses tested bind to MDA5 to inhibit IFN induction[32,69-71]. Rinderpest virus (RPV) may differ, as it appears to use the C protein rather than V to inhibit MDA5 signalling, although the binding of RPV V to MDA5 has not been examined[72]. The V proteins of PIV5, hPIV2, MuV, MeV, NiV, HeV, SeV, Mapuera virus (MPRV), Menangle virus (MenV)

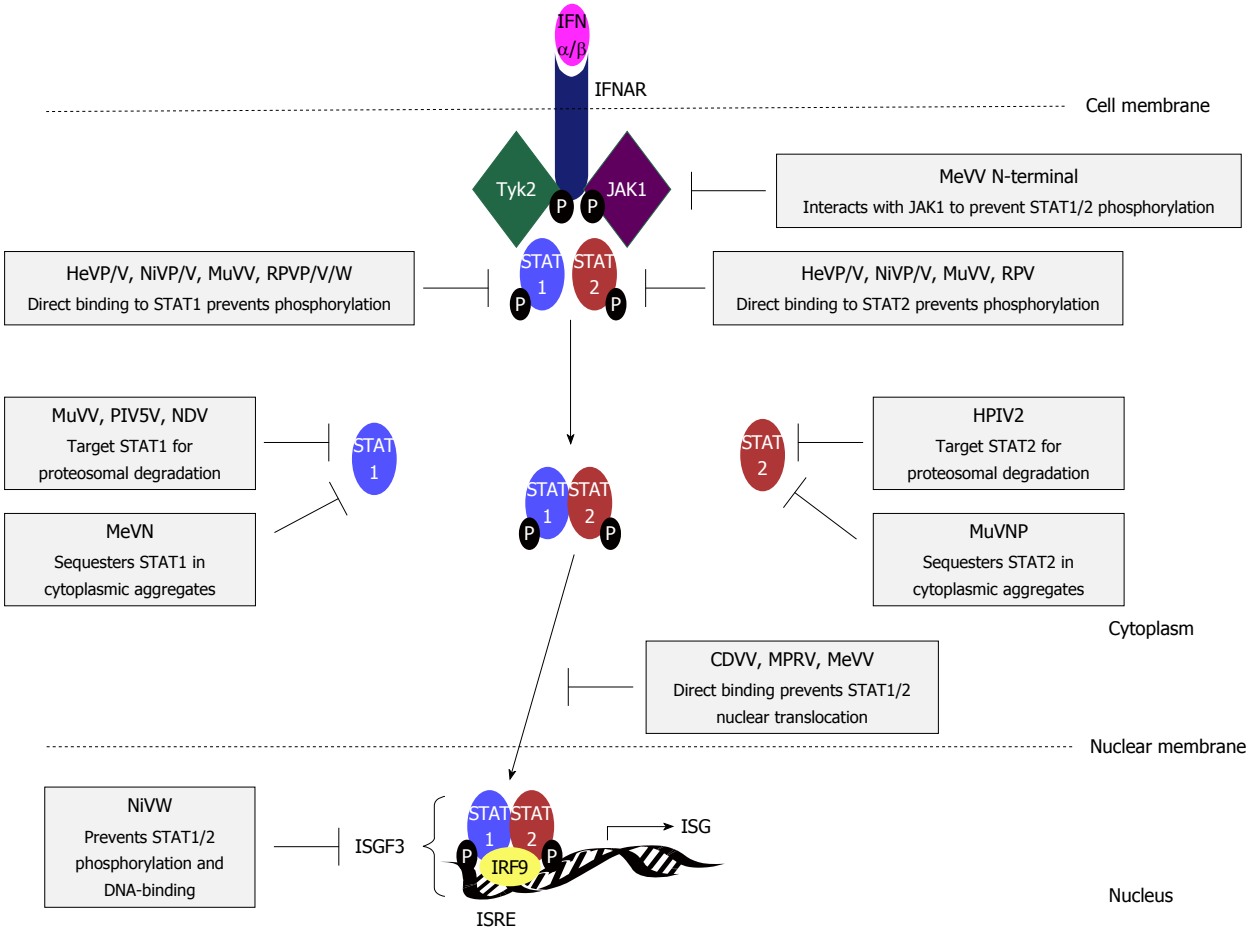

Figure 4 Interferon signalling pathways are targeted by paramyxovirus interferon-antagonist proteins through diverse mechanisms. Interferon (IFN)β binds to type I IFN receptor subunits IFNα/β receptor (IFNAR)1 and IFNAR2, causing dimerization, activation and phosphorylation of the receptor-associated kinases Janus kinase 1 (JAK1) and tyrosine kinase 2 (Tyk2), to create docking sites for the SH2 domains of signal transducers and activators of transcription (STAT)1 and 2. STAT1 and 2 are phosphorylated by Tyk2 and JAK1 respectively, and form a heterodimer that translocates into the nucleus, forming the heterotrimeric transcription factor complex IFN-stimulated gene factor 3 (ISGF3) with IFN regulatory factor (IRF)-9. ISGF3 binding to IFN stimulatory response element (ISRE) sequences in the promoters of hundreds of IFN-stimulated genes (ISGs) activates the transcription of antiviral and immune-modulatory proteins to establish an antiviral state in infected and neighbouring cells, and contribute to shaping the adaptive immune response. STAT1 and/or STAT2 are targeted by almost all paramyxoviruses through the activity of several IFN antagonists by mechanisms that are reported to differ significantly; mechanisms and specific viral proteins responsible are indicated (see text for details). HeV: Hendra virus; NiV: Nipah virus; MuV: Mumps virus; RPV: Rinderpest virus; MeV: Measles virus; PIV5: Parainfluenza virus 5; NDV: Newcastle disease virus; hPIV: Human PIV; CDV: Canine distemper virus; MPRV: Mapuera virus.

and Salem virus (SalV) were shown to bind a specific region within/proximal to residues 701-816 of the MDA5 helicase domain, independently of the MDA5 ligand dsRNA[70,71,73], thereby blocking dsRNA-MDA5 interaction[70]. Although a recent study of PIV5 V identified a change in the dsRNA-binding properties of MDA5 when V was co-expressed, rather than a complete inhibition, suggesting that V may still allow non-cooperative dsRNA binding[74]. In addition, the V proteins of PIV5, MenV, and SalV might have further specialist antagonistic functions, as yeast two-hybrid assays indicated that they interacted with multiple distinct regions of MDA5[70]. A crystal structure of PIV5 V in complex with MDA5 has demonstrated that V unfolds the ATPase domain of MDA5, which allows it to bind a region normally hidden beneath the helicase fold[74]. This unfolding disturbs the ATPase hydrolysis site, and it was shown using MeV V that increasing concentrations of V correlate with decreasing ATPase activity[74].

The MDA5 binding site has been mapped to the C-terminal region of the V proteins of PIV5, MeV, MuV, Newcastle disease virus (NDV), NiV, HeV and SeV[32,69-71,75,76], with conserved residues of the zinc-finger critical to the interaction. However, the precise molecular details differ between specific paramyxoviruses, with conserved cysteine residues in the large zinc finger loop, but not the smaller loop, of PIV5 V and NiV V dispensable for antagonism of IFN induction[32], whereas MuV V and MeV V required all conserved cysteine residues[32]. A crystal structure of MDA5:PIV5 has shown PIV5 V to have six residues (174, 175, 177, 179, 184 and 197) involved in forming the interface with MDA5, only some of which are conserved with other paramyxovirus V proteins[74].

Targeting of RIG-I via laboratory of genetics and physiology 2 protein

In contrast to MDA5, V proteins do not bind directly to RIG-I, nor inhibit RIG-I oligomersation or dsRNA-

binding[70], which has been assumed to indicate that they have no direct role in inhibiting RIG- I activation, but rather target downstream signalling components such as IRF-3 (see below). However, recent data has indicated that V proteins can inhibit RIG- I by interaction with another cellular helicase, the laboratory of genetics and physiology 2 (LGP2)[73], *via* a region of LGP2 homologous to the V protein binding region in MDA5[71,73]. The interaction appears to be dependent on the unique C-terminal domain of V protein, as PIV5 P protein did not bind to LGP2, but the C-terminal domains of MeV and MuV V proteins were necessary and sufficient for the interaction[71,73]. Importantly, V proteins were able to inhibit RIG- I signalling only in cells where LGP2 was coexpressed[73], and RIG- I - LGP2 interaction was detected only in cells expressing V protein, suggesting that V facilitates or mediates this interaction to shutdown RIG- I activation[73]. Because LGP2 is homologous to RIG- I and MDA5, but lacks the CARD domain to activate downstream signalling, it is thought to be a negative regulator of IFN induction, consistent with the inhibitory effects of V protein expression. However, there is evidence that LGP2 can positively regulate IFN induction under some conditions[77-80], so the precise mechanisms of V protein/LGP2 antagonism of RIG- I remain to be determined.

Inhibition of IRF-3 activation

In addition to inhibition of PRRs, paramyxoviruses target downstream signalling components to prevent activation of IRF-3, potentially as a mechanism to inhibit signalling by both RLRs and TLRs (Figure 3). Rubulaviruses including MuV, hPIV2, and PIV5 use V protein as a decoy substrate for the IRF-3 kinases TANK-binding kinase 1 (TBK-1) and inhibitor of NF-κB kinase (IKK)ε (Figure 3), both inhibiting phosphorylation of IRF-3 and facilitating IKKε/TBK-1 polyubiquitination and degradation to prevent further signalling[81].

Henipavirus V proteins do not cause IKKε/TBK-1 degradation[81] or block TLR-3/IRF-3 dependent signalling[76,81]. For henipaviruses, this appears to be a function of the W protein, as NiV W, although having no effect on MDA5 signalling, inhibited TLR-3-dependent phosphorylation of IRF-3[82]. It is possible this is due to binding and sequestration of inactive IRF-3 in the nucleus where NiV W localises, to prevent interaction with cytoplasmic IKKε/TBK-1[82]. This model is consistent with the reported importance of NiV W protein nuclear localisation to its inhibition of TLR3-dependent IFN induction[82]. MeV C protein also inhibits IFN induction, correlating with its nuclear localisation[83], although MeV C does not affect IRF-3 directly, and appears to have an undetermined nuclear target[83]. By contrast, cytoplasmic NDV and SeV V protein bind directly to IRF-3, thereby preventing its nuclear translocation[76]. Thus, paramyxovirus targeting of IRF-3-mediated signalling involves mechanisms that appear to differ significantly between species.

Targeting of STATs by rubulaviruses: degradation and mis-localisation

Almost all rubulavirus V proteins target STAT1 or STAT2 for degradation by the host-cell proteosomal pathways[84-87] through assembly of a V-degradation complex (VDC) containing V protein, STAT1, STAT2, and components of an E3 ubiquitin ligase complex, specifically the UV damage-specific DNA binding protein 1 (DDB1), and Cul4A[88-92], which likely mediate the STAT1/2 polyubiquitination[93]. *In vitro* studies/crystallographic analysis of the PIV5 V-DBB1 complex have indicated that both the N-terminal and unique C-terminal regions of PIV5 V are required for VDC assembly and STAT1 degradation[33,88,93,94]. Intriguingly, although some rubulaviruses target only STAT1 or STAT2 for degradation (see Figure 4 for details)[95,96], both STATs are required, with the non-degraded STAT acting as a "co-factor"[97,98].

The MuV V protein VDC polyubiquitinates and degrades not only STAT1, but also STAT3[84,99], such that MuV V protein can inhibit STAT3-dependent transcriptional activation by IL-6 and v-Src[99]. MuV targeting of STAT3 is independent of STAT1 targeting, as a point mutation abrogating targeting of STAT3 did not affect STAT1[100], and STAT3 degradation does not require the STAT2 "cofactor"[99]. STAT3 targeting by the V protein of MuV is also highly specific to this species, as the V proteins of the rubulaviruses MPRV, hPIV2 and hPIV4 do not reduce cellular levels of STAT3[87,101,102].

Intriguingly, the V proteins of hPIV4a and hPIV4b do not degrade STATs or measurably affect their localisation or phosphorylation, but still bind to STAT1, STAT2 and other VDC components[101]. While these viruses appear to lack the ability to antagonise STAT signalling, the specific binding capacity of the proteins is suggestive of a previous role in STAT antagonism, which may have been lost due to changes in selective pressures[101].

MPRV V protein, by contrast with those of other rubulaviruses, binds to STAT1 and STAT2 to prevent their nuclear translocation without inducing degradation[102]. This is similar to reports for the V proteins of the henipaviruses and morbilliviruses (see below), except in that MPRV V does not inhibit STAT1 phosphorylation and can bind to STAT1 and STAT2 independently[102]. A similar mechanism may be used by the MuV NP protein, which co-localises with STAT2 in punctate aggregates in the cytoplasm of infected cells[99], indicating that NP protein, like P protein, can mediate both replication and IFN antagonist functions.

Targeting of STATs by avulaviruses

In common with rubulaviruses such as PIV5, the avulavirus NDV targets STAT1, but not STAT2, for degradation. Deletion of the C-terminal region of V protein, or deletion of both V and W C-termini by disruption of the RNA editing site, prevented STAT1 degradation by recombinant NDV[95]. As little difference was observed between virus deleted for both V and W, and virus deleted

for the V protein C-terminal domain alone, V protein appears to be the major player, and consistent with this, NDV V but not NDV W degraded STAT1 in transfected cells[95].

Targeting of STATs by morbilliviruses

MeV V binds STAT1 and STAT2 through distinct sites in its N-terminal and C-terminal regions[103], respectively, indicating that targeting of STAT2 independently of STAT1 is important to this virus. MeV V protein does not degrade STATs[104], but has been reported by different laboratories to use several distinct mechanisms, including inhibition of STAT nuclear translocation without affecting STAT phosphorylation[103-105], and inhibition of STAT1 and STAT2 phosphorylation due to interaction of its N-terminal domain with JAK1[106,107]. Canine distemper virus (CDV) and RPV V proteins also inhibit IFN-activated STAT1/STAT2 nuclear import[108,109], with RPV V protein, but not that of CDV, inhibiting STAT1/2 phosphorylation.

MeV V also interacts with IRF-9, which is likely to affect ISGF3 formation (Figure 4)[104], and with STAT3[104], a property thus far restricted in the paramyxovirus family to MeV and MuV V proteins[99,100,104,110]. HeV V and PIV5 V have been shown to lack STAT3 binding function, and while SeV infection can inhibit IFNα-dependent STAT3 phosphorylation, this appears to relate to upstream effects on Tyk2 rather than STAT3 directly[111]. STAT3 binding by other paramyxovirus V proteins, however, has not been investigated.

MeV N protein also inhibits STAT1/2 signalling[112], indicating a particular importance of STAT inhibition to MeV, and co-localises with STAT1 in cytoplasmic aggregates in infected cells, analogously to MuV NP[99,104]. STAT2 also co-localised with MeV N in aggregates, but with reduced frequency compared with STAT1[104].

STAT targeting by respiroviruses: the importance of C proteins

STAT targeting by respiroviruses differs significantly from other paramyxoviruses, due to the expression of additional proteins from the P gene (Figure 2), including four C proteins by hPIV1[14,113], which does not express V or W. The C' protein of hPIV1 binds and sequesters STAT1 in perinuclear aggregates, suggesting that the C proteins may be sufficient for IFN antagonism by this virus[114]. SeV C proteins (C', C, Y1 and Y2), also bind to STAT1 and prevent signalling and, importantly, the functions of the individual C proteins appear non-redundant, as knockout of all four proteins is required to completely prevent IFN antagonism in infected cells[115,116]. Data regarding the mechanisms of SeV C proteins activity are conflicting[116-121], with some reports suggesting that C and C', but not Y1 or Y2, cause STAT1 mono-ubiquitination/degradation[116,117] dependent on the C protein N-termini[118,119], while others reported no reduction in STAT1 expression but indicated inhibition of STAT1 and STAT2 phosphorylation by the C proteins, independently of their N-termini[120,121].

STAT targeting by henipaviruses: the roles of P, V and W

The henipavirus P, V and W proteins can bind to STAT1 and STAT2 through the shared N-terminal region[122,123] to prevent STAT1/2 phosphorylation and activation by holding them in high molecular weight complexes[110,123-125]. Transfection studies indicate that P, V and W have differing capacities to inhibit STAT signalling, with P protein the least effective[125]. This is consistent with the hypothesis that the V and W accessory proteins have evolved to enable specific, distinct roles as IFN-antagonists, sequestering STATs in the cytoplasm and the nucleus, respectively[82,122,125], whereas P protein functions principally as the polymerase cofactor, but can arrest STATs in the cytoplasm. Mutation of the shared G121 residue was found to specifically ablate STAT1 binding by V, W and P, without affecting P protein polymerase cofactor function, enabling the production of recombinant NiV impaired for STAT antagonistic functions to confirm that inhibition of STAT1 phosphorylation in NiV infected cells is due to P/V/W binding[122,126]. In wild-type NiV-infected cells, but not those infected with the mutant NiV, unphosphorylated STAT1 localised exclusively to the nucleus, similar to cells expressing W protein alone, suggesting NiV W has the predominant role in blocking STAT signalling in infected cells[122].

DIFFERENT MECHANISMS OF IMMUNE EVASION: EVOLUTION OR EXPERIMENT?

Although there is abundant evidence that *paramyxovirus P* gene-encoded proteins can antagonise IFN responses by diverse species-specific/genera-specific mechanisms, the source of this diversity is currently unclear. A major caveat of the available data is its heavy reliance on *in vitro* studies, particularly transfection studies of single IFN-antagonist proteins. Although these approaches enable highly specific analyses of the properties of particular IFN-antagonists, including mapping/mutagenesis studies, the potential to generate artefactual data due to the absence of other viral factors and/or non-physiological expression levels is a significant concern. Indeed, several transfection studies in different laboratories have generated conflicting mechanistic data for the same viral protein, including SeV C and MeV V protein[103-107,116,117,120,121], suggesting that some reported differences between IFN antagonists of different paramyxovirus species/genera might arise from experimental rather than biological differences. Importantly, however, recent studies comparing in parallel the functions of V proteins from panels of paramyxoviruses have confirmed clear divergence in specific mechanisms/interactions[70,71,76], indicating genuine divergence at the molecular level.

Recent studies have also directly compared IFN-antagonist protein expression/functions in transfected and

infected cells, identifying clear differences. Notably, one study reported that while henipavirus V and W proteins profoundly inhibit IFN/STAT signalling in transfected cells, no inhibition was apparent in infected cells, which appeared to relate to the higher expression of V/W proteins in transfected cells[127]. This suggested that STAT inhibition by V and W does not have significant roles in infected cells, but it seems unlikely that viruses would evolve proteins that can specifically target factors of the IFN response and impede their function by sophisticated mechanisms were this not important at some stage of infection. While *in vitro* infection approaches are clearly closer to natural infection than transfection, they also use controlled *in vitro* conditions including the inoculation of cultured monolayers of specific cell types with precise multiplicities of infection, and treatments with specific concentrations of IFNs. By contrast, in natural infection the kinetics of viral protein expression and induction of the IFN system is highly dynamic, involving both infected cells and professional IFN-producing cells, and factors such as the infectious dose, route of infection, host species, and infectious spread to specific tissues can vary greatly, significantly affecting requirements for IFN antagonism and the disease outcome[128]. Thus, the diverse mechanisms of IFN antagonism identified in transfection studies may have vital roles in infection *in vivo*.

Importantly, IFN antagonism has been implicated as a key factor in host and tissue specificity, with PIV5 showing limited host range dependent on the capacity of the V protein to bind to STAT2 from different species[129-132], whereas NiV V blocks IFN signalling in cells of many species, consistent with its broad infectious range[82,110,124,126]. Tissue-specific antagonism of IFN has also been reported for NiV, which induces an IFN response in endothelial but not neuronal cells, correlating with differential subcellular localisation of NiV W[133].

A genuine appreciation of the importance of specific IFN-antagonistic mechanisms to pathogenicity, however, requires the use of recombinant virus systems and *in vivo* pathogenicity models. Recent advances in this area include reports that recombinant hPIV2 impaired for V protein antagonism of MDA5 is attenuated in rhesus monkeys[134-136], and that the severity of clinical signs in MeV-infected monkeys was reduced by mutation of the P/V proteins to prevent inhibition of STAT1[137]. In addition, the deletion of V or C proteins from MeV caused attenuation in mice, but V deletion alone resulted in restricted spread in the brain[138], supporting the hypothesis that specific mechanisms of IFN-antagonism are important to infection of certain tissues. Deletion of the V C-terminal domain in recombinant NiV also reduced pathogenicity in a hamster model[123-125,139], possibly due to IFN-antagonist functions of the V C-terminal domain, such as the targeting of MDA5.

Of paramount importance to delineating the roles of specific mechanisms of IFN antagonism in pathogenicity will be the extension of *in vivo* studies to include genetically modified animals deficient in specific IFN signalling processes. For example, recent research indicated that SeV pathogenicity is increased in MDA5 knockout mice[140], suggesting that this might provide a useful model to investigate the importance of MDA5 antagonism in *in vivo* infection.

CONCLUSION

A substantial body of data from the past c. 15 years has provided key insights into the immune evasion strategies of paramyxovirus IFN-antagonists, indicating that they employ a remarkable array of mechanisms to target essential factors of the IFN response, with the limited *in vivo* infection data indicating that these functions are essential to pathogenicity. However, as much of the current mechanistic data comes from *in vitro* transfection approaches, their importance to natural infection remains largely unresolved. Future studies employing *in vivo* infection models, recombinant virus systems and genetically modified animals should begin to unravel in detail the interactions of paramyxoviruses with the IFN system *in vivo*. This is likely to result in the identification of new potential targets for the development of vaccines and antivirals required for the treatment of established prolific human pathogens such as MeV, as well as emerging zoonotic threats including NiV and HeV.

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