V protein, the virulence factor across the family *Paramyxoviridae*: a review

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Abstract. *Paramyxoviridae* is a family of viruses within the order *Mononegavirales* and comprises 14 genera; *Metaavulavirus*, *Orthoavulavirus*, *Paraavulavirus*, *Synodonvirus*, *Ferlavirus*, *Aquaparamyxovirus*, *Henipavirus*, *Morbillivirus*, *Respirovirus*, *Jeilongvirus*, *Narmovirus*, *Salemvirus*, *Pararubulavirus* and *Orthorubulavirus*. The members within this family are negative and single-stranded RNA viruses including human and animal pathogens such as measles virus (MeV), Nipah virus (NiV), mumps virus (MuV), Sendai virus (SeV) and Newcastle disease virus (NDV). The V protein is conserved within the family and plays an essential role in viral pathogenicity. Although V proteins of many paramyxoviruses are interferon-antagonists which counteract with the host's innate immunity, there are still differences in the mode of action of the V protein between different genera or species within the same genera. The strategies to circumvent the host interferon (IFN) pathway can be divided into three general mechanisms; degradation of signal transducers and activators of transcription (STAT) protein, inhibition of phosphorylation of the transcription factor and, inhibition of translocation of STAT proteins into the nucleus. As a result, inhibition of IFN signalling and production promotes viral replication in the host cells. This review highlights the mechanism of the paramyxoviral V protein in evading the host IFN system.

Keywords: *Paramyxoviridae*, *Mononegavirales*, P gene, V protein, interferon, virulence factor

1. Members of the *Paramyxoviridae*

The family of *Paramyxoviridae* belongs to the order *Mononegavirales* and consists of four subfamilies: *Avulavirinae*, *Metaparamyxovirinae*, *Orthoparamyxovirinae*, and *Rubulavirinae* (Adapted from Amarasinghe *et al.*, 2019). A total of 14 genera with three unclassified species were formed as shown in Table 1 (Supplementary). Members of the *Avulavirus* have been reclassified into *Metaavulavirus*, *Orthoavulavirus*, and *Paraavulavirus*; members of the *Rubulavirus* have

also been reclassified into *Orthorubulavirus* and *Pararubulavirus*. For the ease of discussion, the *Avulavirus* and *Rubulavirus* will be used to present members of their respective subfamily. The virions in the family of *Paramyxoviridae* are mainly spherical with a diameter of 150 nm to 300 nm but they can be filamentous and pleomorphic as well (Takimoto and Portner, 2004; Harrison *et al.*, 2010). The genetic material of the viruses consists of single-stranded, negative-sense and non-

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segmented RNA. Their natural hosts range from humans (such as the measles virus) to animals (such as the Newcastle disease virus) (Young *et al.*, 2000; Ganar *et al.*, 2014).

1.1 Genomic content of *Paramyxoviridae*

Although the members of the *Paramyxoviridae* are highly diverse, they share a common genome structure. The genome starts with a 3' leader sequence of approximately 50 nucleotides and ends with a 5' trailer region (Fearn and Plemper, 2017). Both the leader and trailer sequences are untranslated regions which are involved in viral replication and genome packaging (Yan and Samal, 2008). The paramyxoviruses contain six main genes which are nucleocapsid (N), phosphoprotein (P), matrix (M), fusion (F), attachment (G/H/HN) and polymerase (L) that encode for six structural proteins, respectively (Audsley and Moseley, 2013). The genes are flanked with conserved regions known as gene start, intergenic region and gene end (Fearn and Plemper, 2017). The arrangement of the genes in the genome is shown in Figure 1. Firstly, the gene that is closest to the 3' end of the genome is the N gene that encodes the nucleocapsid protein (NP) which binds to the viral RNA and protects the genome from nuclease digestion (Choppin and Compans, 1975; Yusoff and Tan, 2001). The RNA genome follows the rule-of-six where one nucleocapsid protein will encapsidate six nucleotides to allow efficient replication by viral polymerase (Calain and Roux, 1993). The genomic RNA and NP forms a helical ribonucleoprotein (RNP) complex that is recognized by the viral RNA-dependent RNA polymerase, which is made up of P protein and L protein (Ganar *et al.*, 2014; Cox and Plemper, 2017). The L protein exhibits the catalytic activities of polymerase whereas the P protein facilitates the binding of P-L complex to nucleocapsid (Dortmans *et al.*, 2010; Fearn and Plemper, 2017). The matrix gene encodes for the highly hydrophobic and basic matrix (M) protein (Chambers *et al.*, 1986; Yusoff and Tan, 2001). M proteins are located between the nucleocapsid and the inner surface of the lipid envelope (Ganar *et al.*, 2014). These proteins aid in virus assembly and virus budding through interaction with the host

plasma membrane (Harrison *et al.*, 2010; Ganar *et al.*, 2014).

The genome of paramyxoviruses encodes for two transmembrane glycoproteins, the fusion (F) protein and the attachment protein. These proteins are encoded by different genes in different genera. For example, the attachment protein for *Rubulavirus* and *Avulavirus* is encoded by the haemagglutinin-neuraminidase (HN) gene; *Respirovirus* and *Morbillivirus* have haemagglutinin (H) gene for their attachment protein whereas glycoprotein (G) protein is encoded by *Henipavirus* (Harrison *et al.*, 2010). These surface glycoproteins present on the viral envelope as 'tiny spikes' projecting from the outermost layer of the virion (Yusoff and Tan, 2001; Ganar *et al.*, 2014). The last gene to undergo transcription upon viral replication is the L gene that codes for the L protein (Yusoff *et al.*, 1987; Ganar *et al.*, 2014). Besides being part of the viral polymerase, the L protein also carries out post-transcriptional modification such as 5' capping, methylation, polyadenylation on the newly synthesised mRNA (Dortmans *et al.*, 2010).

Figure 1. The 3'-5' genomic RNA of paramyxoviruses with boxes represent the open reading frame (ORF) of viral proteins. Multiple ORFs that present within a gene are indicated by a slash (/) (Modified from MacLachlan and Dubovi, 2017).

Depending on the genus, the P gene also encodes additional protein apart from the P protein (Ganar *et al.*, 2014; Young *et al.*, 2000). The P gene of *Avulaviruses* encodes for V and W proteins at the same time (Young *et al.*, 2000; Mebatsion *et al.*, 2001). Whilst the P mRNA is a constant transcript for the P gene in *Avulavirus*, *Respirovirus*, *Henipavirus* and *Morbillivirus*, the generation of the V and W mRNA requires

addition of non-templated guanine (G) residue(s) (+1 frameshift and +2 frameshift, respectively) (Steward *et al.*, 1993; Young *et al.*, 2000). The frequencies of production of the P, V, and W proteins that are derived from the P gene in *Avulaviruses* are estimated to be at 68%, 29%, and 5% respectively (Mebatsion *et al.*, 2001). On the other hand, the *Respirovirus*, *Henipavirus*, and *Morbillivirus* encode both the V and C proteins within the open reading frame of P gene (Young *et al.*, 2000; Parks and Alexander-Miller, 2013). In *Rubulavirus*, the V protein is produced from the P gene. The V mRNA is an invariable product from the P gene. Apparently, the production of the P mRNA requires insertion of two non-templated guanine (G) residues (+2 frameshift) (Steward *et al.*, 1993; De Leeuw and Peeters, 1999; Young *et al.*, 2000). *Rubulaviruses* do not encode the C protein but they have a small hydrophobic (SH) gene which is located between the F and HN genes (De Leeuw and Peeters, 1999).

Figure 2. The coding strategies of paramyxoviruses to generate P and V protein. The V protein shared the identical N-terminal protein sequences with P protein but different C-terminal (highlighted in blue) due to addition of non-template guanine residue(s) at the RNA editing site. Production of V mRNA from P gene requires additional of one guanine residue (+1 G) in *Morbillivirus*, *Henipavirus*, *Respirovirus* and *Avulavirus* whereas V mRNA is a constant transcript in *Rubulavirus* and P mRNA is generated through two guanines insertion (+2 G).

These proteins (P, V and W proteins) from the P gene share the same amino (N) terminal but different carboxyl (C) ends in terms of the length and amino acid constituents (Figure 2) (Huang *et al.*, 2003). The mechanism to generate mRNA that encodes for the P, V and W proteins is known as RNA editing at the conserved editing site through addition of G nucleotides in the open reading frame of P protein (Steward *et al.*, 1993; Parks and

Miller, 2013). The V protein of NDV, parainfluenza virus 5 (PIV-5) and mumps virus are found to be a structural constituent incorporated into the virions but the V proteins of Sendai virus and measles virus are not incorporated into the virions (Curran *et al.*, 1991; Paterson *et al.*, 1995; Steward *et al.*, 1995; Patterson *et al.*, 2000). The V proteins function as an interferon-antagonist in paramyxoviruses and they are considered as accessory proteins of the P gene (Gotoh *et al.*, 2001; Audsley and Moseley, 2013).

2. Evading cellular anti-viral response

2.1 Interferon signalling overview

Interferons (IFN) are the main cytokines or signalling molecules involve in the first line of host defence system also known as innate immunity against viral infections. The main function of IFN is to establish an antiviral state among uninfected cells through transcription of antiviral genes as well as induce apoptosis in infected cells to stop virus replication (Tanaka *et al.*, 1998; Huang *et al.*, 2003; Parks and Alexander-Miller, 2013). IFN can be classified into type one (IFN-I) and type two interferon (IFN-II). IFN-I consists of IFN- α and IFN- β which are produced in cells upon viral infection (Tanaka *et al.*, 1998). IFN-II comprises IFN- γ and is confined to mitogen or cytokine activated lymphoid cells such as T helper cells, cytotoxic T cells and natural killer (NK) cells (Samuel, 2001; Tanaka *et al.*, 1998). The response of IFN-I signalling pathway towards viral infection will be discussed in this review.

Figure 3 shows the regulation of IFN signalling in the cell. The cell surface receptor for IFN-I is made up of two subunits which are IFNAR-1 and IFNAR-2. Binding of IFN to their respective receptors will cause the latter to undergo heterodimerisation (Samuel, 2001). Stimulation of different types of IFN will lead to activation of different Janus family of tyrosine kinases (JAK) (Tanaka *et al.*, 1998). For instance, IFNAR-1 subunit will interact with TYK2 whereas IFNAR-2 will interact with JAK1. After that, the underlying cytoplasmic signal transducers and activators of transcription (STAT) proteins are phosphorylated by JAK

enzymes (Qiu *et al.*, 2016). IFN-I stimulates the formation of heterotrimer IFN-stimulated gene factor 3 (ISGF-3) consisting of phosphorylated STAT1, STAT2, and interferon regulatory factor 9 (IRF-9), which is also known as p48 protein (Samuel, 2001). These structures are then translocated into the nucleus where they will bind to the cis-acting DNA elements, IFN-stimulated response element (ISRE), to further transcribe IFN inducible genes (Samuel, 2001; Qiu *et al.*, 2016). Among the interferon-induced anti-viral proteins are double-stranded RNA activated protein kinase (PKR), 2', 5'-oligoadenylate

synthetase (OAS), and the Mx proteins (Clemens, 1997; Floyd-Smith *et al.*, 1981; Haller *et al.*, 1998). Evasion of pro-apoptotic mechanism of host cell is required to allow successful viral replication and spreading of progenies in a cell (O'Brien, 1998; Roulston *et al.*, 1999). Through evolution, many paramyxoviruses have established strategies to counteract the antiviral response induced by IFN. One of the accessory proteins, the V protein, that is a common IFN antagonist across *Paramyxoviridae* and its mechanism interacting with the host IFN pathway will be discussed further.

Figure 3. Regulation of IFN signalling through Janus kinase (JAK) - signal transducer and activator of transcription (STAT) pathway. Binding of IFN to type I interferon receptor leads to the activation of TYK2 and JAK1 kinase. STAT proteins are then phosphorylated and dimerised, followed by forming a complex called IFN-stimulated gene factor 3 (ISGF-3) with interferon regulatory factor 9 (IRF-9). The ISGF-3 translocates into the nucleus and binds to the IFN-stimulated response element (ISRE) to initiate the transcription of targeted genes.

2.2 Biological role of V protein of paramyxoviruses

2.2.1 Mumps virus (MuV), parainfluenza virus 5 (PIV-5) and human parainfluenza virus type 2 (HPIV-2) from genus *Orthorubulavirus*

MuV targets STAT1 and STAT2 to prevent activation of the IFN signalling in cells. It was found that cells persistently infected with MuV experienced a loss of STAT1 protein despite being treated with IFN and proteasome inhibitors (Yokosawa *et al.*, 1998). Kubota *et al.* (2002) demonstrated that the V protein is able to bind to receptor-activated C kinase (RACK1), which is an adaptor to facilitate the binding of STAT1 protein to the IFN receptor. It was also shown that STAT1 is able to interact with MuV instead of RACK1. As a result, the interaction between STAT1 and IFN receptor is inhibited. This may be the reason why IFN signalling can be inhibited prior to STAT1 protein degradation (Kubota *et al.*, 2005). Moreover, the C terminal of MuV V protein is capable of inhibiting the tyrosine phosphorylation of both the STAT1 and STAT2 instead of only targeting STAT1 degradation (Kubota *et al.*, 2005). Besides, a tryptophan-rich motif in the cysteine rich C terminus of the MuV V protein is also responsible for ubiquitination and degradation of STAT1 (Nishio *et al.*, 2002; Yokosawa *et al.*, 2002). The complete abolishment of the V protein in MuV led to high induction level of a proinflammatory cytokine, interleukin-6 (IL-6) attracting monocytes to the site of infection quickly and attenuating the MuV (Xu *et al.*, 2012).

The V protein of PIV-5, formerly known as simian virus (SV5), was found to block the IFN signalling by proteasomal degradation of STAT1 protein in human, murine and canine cells (Didcock *et al.*, 1999; Young *et al.*, 2001; Chatziandreou *et al.*, 2004). According to Precious *et al.* (2005), the V protein links UV-damaged DNA-binding protein (DDB1), STAT1, STAT2, and Cullin 4a to form a ubiquitin ligase complex, which is involved in the ubiquitination of the STAT1 protein. In the absence of STAT2 protein in the ubiquitin ligase complex, the STAT1 protein will not be ubiquitinated for degradation. This interferon antagonistic activity is contributed by the C-terminus of V protein because the IFN- β induction is higher in cells infected with

recombinant PIV-5 (C terminal deficient) as compared to the infection with wild type PIV-5 (Poole *et al.*, 2002). As a result of STAT1 protein degradation, formation of ISGF-3 and gamma activation factor (GAF), a homodimer of phosphorylated STAT1, is inhibited causing the breakdown of signals to establish an antiviral state to suppress virus replication (Didcock *et al.*, 1999). In other words, PIV-5 and MuV are capable of inhibiting both type I and type II IFN (Young *et al.*, 2000). Unlike MuV, recombinant PIV-5 without V protein expression could not be recovered (He *et al.*, 2002). This observation suggested that V protein might play a role in viral replication in PIV-5 as compare to MuV (Xu *et al.*, 2012).

Andrejeva *et al.* (2004) showed that the V protein of PIV-5 as well as the other paramyxoviruses such as HPIV-2, SeV, MuV and HeV, interacts with melanoma differentiation-associated gene 5 (MDA-5), a RNA helicase with a caspase recruitment domain (CARD) at its amino end that is inducible by the host IFN. The interaction between the helicase and C terminal of V protein represses the activation of both NF- κ B and IRF-3 which is the transcription factor that binds to IFN- β promoter upon detection of polyinosinic polycytidylic acid (poly I:C), the synthetic analogue for dsRNA (He *et al.*, 2002; Poole *et al.*, 2002; Childs *et al.*, 2007). Although the viral genome from *Paramyxoviridae* is ssRNA, dsRNA appears to be the replicative intermediate in infected cells (Jacobs and Langland, 1996). Hence, the V protein of paramyxoviruses can limit the intracellular dsRNA signalling that triggers the IFN transcription (Poole *et al.*, 2002; Childs *et al.*, 2007).

On the other hand, HPIV-2 from *Rubulavirus* blocks the IFN signalling by proteolytic degradation of STAT2 protein instead of STAT1 protein (Young *et al.*, 2000; Parisien *et al.*, 2001). Since STAT2 protein is a component of ISGF-3 that will later bind to ISRE in the promoter of IFN I inducible genes, type I IFN will be blocked due to the loss of STAT2 protein (Parisien *et al.*, 2001).

In short, although the IFN signalling is initiated upon viral infections, time is taken to degrade the STAT proteins. For example, the STAT1 protein in PIV-5 infected cells degrade completely at least 12 h post-infection (Didcock *et*

al., 1999). Moreover, near complete degradation of the STAT2 protein in HPIV-2 infected CV1, a monkey kidney cell line occurs at 9 h post-infection (Parisien *et al.*, 2001). In CV1 and Vero cells infected by MuV, STAT1 degradation is more time consuming since more than 50% of the STAT1 protein is still present after 24 h post-infection as compared to uninfected cells (Kubota *et al.*, 2005). Hence it was proposed that *Rubulaviruses* might have other mechanisms than protein degradation to antagonise the host IFN pathway.

2.2.2 Newcastle disease virus (NDV) from genus *Orthoavulavirus*

The IFN system of avian cell during NDV infection is ineffective due to the presence of the V protein which degrades the STAT1 protein (Huang *et al.*, 2003). Qiu *et al.* (2016) showed that the V protein selectively targets the phosphorylated STAT1 protein for ubiquitin-mediated proteolytic degradation. Hence the total level of STAT1 protein is reduced due to the decrease of phosphorylated STAT1 protein. The C terminal of the V protein is responsible for IFN antagonistic activity similar to that of the C terminal of V protein in MuV and HPIV-2 (Huang *et al.*, 2003).

The V protein of NDV can also prevent apoptosis in avian cells and thus enhance the virus replication in host cells with a complete IFN system (Mebatsion *et al.*, 2001; Park *et al.*, 2003a; Huang *et al.*, 2003; Chu *et al.*, 2018). This property of the V protein contributes to the specific host range of NDV (Park *et al.*, 2003a). Later, Chu *et al.* (2018) found that the V protein targets the host Calcyclin-Binding Protein and Siah-1 Interacting Protein (CacyBP/SIP) to inhibit cell apoptosis in chicken embryo fibroblasts (DF-1) cells through Caspase 3 pathway. Topolskwo *et al.* (2016) showed that the function of the CacyBP/SIP is associated to dephosphorylation of protein, ubiquitination, cytoskeletal dynamics, and some of the cellular processes such as gene expression, cell proliferation, differentiation, and tumourigenesis. As a result, virus replication is promoted in NDV infected cells.

Besides, recombinant NDV lacking V protein expression is found to be less pathogenic than the parental wild type NDV based on pathogenicity

studies such as mean death time (MDT), intracerebral pathogenicity index (ICPI) and intravenous pathogenicity index (IVPI) (Huang *et al.*, 2003). According to Park *et al.* (2003a), when the NS1 gene from influenza A virus is inserted into a recombinant NDV with carboxyl end deficient V protein, the virus replication in embryonated eggs and chicken embryo fibroblast is restored and is comparable to that of the wild type NDV. Hence it can be concluded that the influenza NS1 protein is having the same function as V protein of NDV where both of them act as interferon antagonist.

2.2.3 Measles virus (MeV) from genus *Morbillivirus*

The V protein of MeV was found to interrupt the translocation of both STAT1 and STAT2 proteins to the nucleus after IFN- α treatment (Palosaari *et al.*, 2003). In addition, the phosphorylation of STAT proteins is inhibited but they are not prone to degradation (Takeuchi *et al.*, 2003). The N terminal of V protein interacts with STAT1 and JAK1 whereas zinc domain in C terminus of V protein facilitates the binding between the V protein itself and the STAT2 protein (Caignard *et al.*, 2007; 2009). Therefore, the V protein of MeV interferes with IFN- α , β and γ signalling (Takeuchi *et al.*, 2003; Caignard *et al.*, 2009).

On the other hand, the P protein of MeV blocks the STAT1 phosphorylation and co-localises with STAT proteins in the cytoplasm. The P protein interacts with the linker domain and SH2 domain of STAT1 protein resulting in the inhibition of STAT1 phosphorylation by JAK1 (Devaux *et al.*, 2013). Apparently, tyrosine 110 at the N terminal of P protein contributes to this cytoplasmic retention or sequestration of STAT1 protein in MeV (Devaux *et al.*, 2007).

In addition, the IFN exhibits both autocrine and paracrine properties where its transcription in virus infected cells will produce a positive feedback loop in these cells as well as the uninfected neighbouring cells as shown in Figure 3 (Samuel, 2001; Perry *et al.*, 2005). Plasmacytoid dendritic cell precursors (pDCs) is the primary type I IFN producer expressing high level of TLR7 and TLR9 but not TLR2, 3, 4, 5 and 8 within the endosome (Liu, 2005). The ligand for

TLR7 is a single stranded viral RNA whereas the ligand for TLR9 is unmethylated CpG DNA motifs on viruses and bacteria (Hemmi *et al.*, 2000; Diebold *et al.*, 2004; Heil *et al.*, 2004; Lund *et al.*, 2004). Upon detection of RNA viruses, TLR7 and TLR9 utilise an adaptor molecule myeloid differentiation factor-88 (MyD88) to transmit downstream IFN signalling (Perry *et al.*, 2005). MyD88 will form a complex with tumour necrosis factor receptor-associated factor-6 (TRAF6), IRF7, interleukin-1 receptor-associated kinase (IRAK-1) and IRAK-4 in the cytoplasm (Honda *et al.*, 2004; Kawai *et al.*, 2004; Hengel *et al.*, 2005). In this complex, E3 ubiquitin ligase activity of TRAF6 activates IRF7 (Honda *et al.*, 2004; Kawai *et al.*, 2004). Besides IRAK, I κ B kinase α (IKK α) was also shown to phosphorylate IRF7 (Hoshino

et al., 2006). When IRF7 is activated by phosphorylation, it homodimerises and translocates into the nucleus to bind to the promoter of IFN-I and induce their expression (Honda *et al.*, 2004; Kawai *et al.*, 2004; Pfaller and Conzelmann, 2008). However, Pfaller and Conzelmann (2008) found that the C terminus of MeV V protein will bind to IKK α and IRF7 and result in inhibition of IFN induction through TLR7/9 and MyD88-mediated pathway. Thus, the V protein becomes a decoy substrate for IKK α where it competes with IRF7 to get phosphorylated by IKK α . Nevertheless, the MeV V protein could not impair the IFN induction involving TBK1 and the related IKK ϵ .

Figure 4. Type I IFN activation pathway. Paramyxoviruses are RNA viruses that enter the host cytoplasm through endocytosis. The Toll-like receptors (TLR) will interact with the pathogen-associated molecular patterns (PAMPs) which are the genetic material of viruses followed by activating the transcription factors interferon regulatory factor (IRF) to translocate into the nucleus and stimulate type I IFN transcription.

2.2.4 Nipah virus (NiV) and Hendra virus (HeV) from genus *Henipavirus*

The V protein for NiV and HeV in *Henipavirus* is known for the largest V protein across *Paramyxoviridae* where they share high similarities of amino acids sequence (Rodriguez and Horvath, 2004). They antagonise the host IFN system by binding the V proteins to both STAT1 and STAT2 proteins, to form a large trimeric complex (Rodriguez *et al.*, 2002; 2003). The V protein has to bind to STAT1 proteins prior to interacting with STAT2 proteins (Rodriguez *et al.*, 2004; Basler, 2012). This complex will be sequestered in the cytoplasm, preventing the STAT proteins from translocating into the nucleus. The peptide sequence on V proteins known as CRM1-dependent nuclear export signal (NES) allows the V protein to move into the nucleus and bind to the STAT proteins and translocate them out from the nucleus, resulting in retention of STAT proteins in the cytoplasm (Rodriguez *et al.*, 2004; Rodriguez and Horvath, 2004). Recently, the N protein of NiV is also found to inhibit IFN signalling by preventing the STAT complex formation. As a result, translocation of activated STAT proteins from the cytoplasm to the nucleus is prohibited (Sugai *et al.*, 2017). In addition, the V proteins inhibit the tyrosine phosphorylation of STATs proteins, but like that of the MeV, the STAT proteins are not degraded. As a result, the IFN signalling is inhibited (Rodriguez *et al.*, 2002). While the IFN antagonistic activity of other paramyxoviruses is correlated with cysteine rich C terminal of V protein, Park *et al.* (2003b) revealed that the IFN antagonistic property of Nipah virus is contributed by the N terminal of the V protein. The glutamic acid at residue 125 of NiV V protein seems to be contributing to IFN antagonism as well (Hagmaier *et al.*, 2006). As compared to V protein, W protein are more effective at blocking activation of the ISG54 promoter, a promoter that can be activated by IRF-3 or IFN-induced transcription factor ISGF3 through the TLR3 signalling pathway (Shaw *et al.*, 2005). According to Yoneda *et al.* (2010), Both the V and C proteins of Nipah virus are responsible for the virulence *in vivo* while the W protein does not. Besides, the C

termini of the V protein for these two viruses were found to interact with the helicase domain of MDA-5 as well to suppress the IFN- β transcription (Andrejeva *et al.*, 2004; Childs *et al.*, 2007). The ability of NiV to suppress RIG-I and MDA5-dependent interferon signalling is defined by the stabilisation of a regulator namely UBX domain-containing protein 1 (UBXN1) by the V protein (Uchida *et al.*, 2018).

In short, STAT proteins are essential components to facilitate IFN activity. This is because expression and activation of IFN-induced genes require phosphorylation of STAT1 and STAT2 by JAK family (Qiu *et al.*, 2016). However, STAT proteins often become the common target for paramyxovirus V protein. Upon interacting with the V protein, STAT proteins lose their ability to transmit the downstream IFN signalling. As a result, transcription of IFN-stimulated genes will be greatly reduced. In short, an impaired IFN system will turn down the viral resistance in the host cells which lead to rapid and successful multiplication of virus (Hengel *et al.*, 2005). The strategy of *Paramyxoviridae* to counteract with the component of IFN system is summarised in Figure 5.

3. The antagonistic activities of V protein carboxyl terminal

The C terminal of the paramyxovirus V protein is known to have contributed to the IFN antagonistic activity (Liston and Briedis, 1994; Paterson *et al.*, 1995; Steward *et al.*, 1995; Huang *et al.*, 2003; Park *et al.*, 2003a; Qiu *et al.*, 2016). It has seven conserved cysteine residues that can interact and formed a unique zinc finger fold with an invariant histidine (Figure 6). The zinc finger consists of two loops with different length and bounded with two zinc atoms per protein chain (Paterson *et al.*, 1995; Steward *et al.*, 1995; Ramachandran and Horvath, 2010). The integrity of the C terminal of V protein is important for its biological activity and any mutation on the cysteine residue will result in protein and biological activity dysfunctionality (He *et al.*, 2002).

Figure 5. Inhibition of IFN-I signalling pathways by paramyxoviruses. The V protein of MuV and PIV-5 directs STAT1 protein for proteasomal degradation whereas HPIV-2 V protein targets STAT2 protein degradation. Besides, NDV V protein selectively binds to phosphorylated STAT1 protein for ubiquitin mediated proteolytic degradation. MeV blocks the translocation of both STAT proteins into nucleus. Next, the V protein of MeV, NiV and HeV inhibits the tyrosine phosphorylation of STATs protein. Meanwhile, V protein of NiV and HeV from *Henipavirus* sequesters STAT1 and STAT2 proteins in cytoplasm by forming a large trimeric complex that is consist of both STATs proteins and V protein. Hence the displacement of STAT proteins into the nucleus is prohibited.

Figure 6. Amino acid sequence alignment in carboxyl terminal of V protein from different genus in the family *Paramyxoviridae*. The N terminal of the open reading frame is omitted and only the conserved region is shown with the amino acid residue number. The conserved seven cysteine residues are numbered and marked with asterisks above together with the conserved histidine that involved in zinc-binding. The example of virus is indicated next to the genus. AsaPV: Atlantic salmon paramyxovirus; FDLV: Fer-de-Lance virus; MuV: Mumps virus; PIV-5: Parainfluenza virus 5; HPIV-2; Human parainfluenza virus 2; NDV: Newcastle disease virus; SeV: Sendai virus; HeV: Hendra virus; NiV: Nipah virus; MeV: Measles virus (Modified from Audsley and Moseley, 2013).

Mutation of the second cysteine of V protein by substitution to other amino acid will abolish the MDA interference by NiV and PIV-5 whereas mutation of the first cysteine will still retain the V protein activity (Ramachandran and Horvath, 2010). In contrast, all the cysteine residues are required in order to maintain the interaction of MDA and the V protein of mumps virus and measles virus (Ramachandran and Horvath, 2010). In addition, the first conserved arginine residue present at the carboxyl terminal of the V protein is found to interact with MDA5 resulting in the interference of the MDA5 signal transduction in diverse paramyxoviruses such as PIV-5, MuV, MeV and NiV (Ramachandran and Horvath, 2010). The interaction between the V protein C terminal with RIG-I and TRIM25 is conserved in different genera within the *Paramyxoviridae* such as NiV, SeV, MeV and PIV-5 to inhibit downstream RIG-I signalling (Sánchez-Aparicio *et al.*, 2018).

Besides, substitution of cysteine with alanine at position 189, 207 and 214 in mumps virus causes the reduction of proteasome-mediated degradation of STAT1 (Kubota *et al.*, 2002; Yokosawa *et al.*, 2002). Furthermore, paramyxovirus such as MuV, HPIV-2, SV5 and MeV requires a V protein with intact C terminal in order to interact with DDB1. Any substitution of cysteine residues to another amino acid will disrupt this interaction (Lin *et al.*, 1998).

In the case for NDV, the C terminal of the V protein is responsible for the interaction with CacyBP/SIP in order to prevent apoptosis (Chu *et al.*, 2018). In 2010, Alamares *et al.* showed that there are four amino acids differences at the C terminal of V protein between lentogenic and mesogenic NDV strain where each residue has an effect on IFN antagonism. The virulence patterns of the V protein among the different NDV pathotypes was further investigated by Wang *et al.* (2019). Their studies revealed that the V protein from different NDV pathotypes will exhibit different levels of interferon antagonistic activity. For example, the V protein of velogenic NDV showed the most reduction in IFN- β expression in NDV infected cells. Although NDV with same pathotypes share higher homology in amino acid sequence, the exact function of individual amino acids towards the interferon antagonism can only be known through the construction of

recombinant NDV with specific V protein mutation (Wang *et al.*, 2019).

In a conclusion, the ability to antagonise the host IFN system is important for viral pathogenesis. Further studies are required to determine the interaction between host proteins and the V proteins particularly in regulating the paramyxovirus replication (Chu *et al.*, 2018). Finally, it is hoped that this review is able to convey a true understanding of the role of V protein as a virulence factor among paramyxovirus. Further analysis of viral anti-IFN strategies together with the mode of action of multiple virulence factors is definitely required not only from the perspective of *in vitro*, but the behaviour in natural infection as well.

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