Review Article

PPRV-Induced Immunosuppression at the Interface of Virus-Host Interaction

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Abstract | Peste des petits ruminants virus (PPRV) is the causal agent of a highly contagious disease that affects domestic and wild small ruminants, Peste des petits ruminants (PPR). Due to the important economical losses caused by this virus in Africa and Asia, the development of more effective, targeted and successful treatments for the disease are necessary. Like other Morbilliviruses, PPRV induces a suppression of the immune system during the acute disease, which favours the establishment and exacerbates the progression of secondary infections. This review gives an overview of the known immunosuppressive strategies of PPRV, among the Paramyxoviruses, as well as the strategies developed by this virus to evade the immune system, focusing on the newly identified factors involved. In the last years substantial progress has been reported in the identification of viral factors involved in the host immunosuppression, although future studies employing *in vivo* infection models are needed to clearly understand the mechanisms developed by these viruses, in particular PPRV, to interact with the host immune system. A better comprehension of this behaviour could lead the global strategy for the control and eradicaton of PPR, initiated by Food and Agriculture Organization of the United Nations (FAO) and World Organisation for Animal Health (OIE) on 2015.

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Viruses use different strategies to avoid immunosurveillance that include the induction of immunosuppression. While immunosuppression provides the infecting pathogen with the opportunity to maximize their chances of survival, replication and transmission, the clinical consequences on the host may be severe. Thus, the generalized immunosuppression induced by viral infections is often associated with secondary infections with related or unrelated viral or bacterial infections, being a serious clinical problem. Understanding the different mechanisms involved in the induction in immunosuppression is crucial for controlling important human and animal pathogens.

Peste des petits ruminants (PPR) is an acute and highly contagious disease that affects domestic and wild small ruminants, sheep and goats (Abraham et al., 2005; Ozkul et al., 2002). Infections in goats are typically more severe than in sheep, although some sheep populations can be highly susceptible (Shaila et

al., 1989; Yesilbağ et al., 2005). In cattle, the disease is asymptomatic and not transmitted to other animals. Seroprevalence in camels and water buffalos has also been reported (Govindarajan et al., 1997; Saeed et al., 2010). Because of the high mortality and severe morbidity rates it causes and its prevalence in developing countries, PPR is an economical relevant disease for livestock and represents one of the main constraints in improving small ruminant productivity. Clinically, PPR infections vary from acute with severe clinical disease and death, to mild with little or no visible clinical signs. Acute infection can produce severe pyrexia with affected animals often becoming restless, having a dull coat, dry muzzle, mucopurulent nasal and ocular discharges, coughing, diarrhoea, enteritis, pneumonia and loss of appetite (Gargadenned and Lalanne, 1942; Lefèvre and Diallo, 1990).

PPR is caused by a Morbillivirus (Gibbs et al., 1979), peste des petits ruminants virus (PPRV) (Lefèvre and Diallo, 1990), that belongs to the Paramixoviridae family, order Meganoviridae. This large family of negative single-strand, enveloped RNA viruses, causes a number of relevant human and animal diseases. It currently includes seven known members: measles virus (MeV), Rinderpest Virus (RPV), PPRV, canine distemper virus (CDV), phocine distemper virus (PDV), cetacean Morbillivirus (CeMV) and feline Morbillivirus (FMV) (Woo et al., 2012). The structural and genetic elements are common in all these viruses. The Morbillivirus genome is a single-strand RNA molecule that encodes six structural proteins: two transmembrane glycoproteins sited in the viral envelop, the fusion (F) and the hemagglutinin (H), an helical nucleocapsid with the nucleoprotein (N) enveloping the RNA in combination with the phosphoprotein (P) and the viral polymerase (L) that form the ribonucleoprotein complex (RNP); and on the inner surface of the envelope, the matrix protein (M) that bridges the cytosolic tails of the F and H to the RNP. The viral RNA also encodes for two non-structural proteins C and V, and a putative protein W. Morbillivirus have been shown to be polyploid (Rager et al., 2002).

As other Morbillivirus, PPRV induces a suppression of immune functions during the acute disease (Rojas et al., 2014), which favours the establishment of and aggravates the course of secondary infections. Concomitant with this immunosuppression, a virus-specific immune response is generated which essentially clears the virus and allows the development of a long-lasting immune response. In this review, we will give an overview of the known immunosuppressive strategies of PPRV. We will discuss the cellular mechanisms of PPRV infection leading to immunosuppression, comparing them to other Morbillivirus. Moreover, the molecular mechanisms that PPRV uses to block immune related signalling are considered and contrasted with better-studied viruses (e.g. MeV) to provide a broader view of possible immunosuppressive strategies used by the virus.

Viral Infection, Dissemination and Cellular Immunosuppression

PPRV Experimental Infections

Typically, PPRV infections occur through the respiratory tract. In susceptible animals it leads to lesions in the respiratory tract, the gastrointestinal tract and in lymphoid organs (Kumar et al., 2004; Pope et al., 2013; Truong et al., 2014). Natural PPRV infections resemble those of other Morbillivirus and result in acute pneumonia and severe gastroenteritis (Chowdhury et al., 2014; Kul et al., 2007), producing an immunosuppression accompanied with leucopenia (Jagtap et al., 2012; Pope et al., 2013; Rojas et al., 2014). Over the years, experimental infections have been carried out in laboratory to better analyze early infection events (Baron et al., 2014; Couacy-Hymann et al., 2007, 2009; Hammouchi et al., 2012; Harrak et al., 2012; Kumar et al., 2004; Pope et al., 2013; Rajak et al., 2005; Truong et al., 2014; Wernike et al., 2014). Early studies often used subcutaneous inoculation, which recapitulated natural clinical signs quite accurately (Couacy-Hymann et al., 2007; Kumar et al., 2004). A comparative study of experimental administration routes indicated that clinical sign apparition was similar when inoculations were intranasal, intravenous or subcutaneous (Harrak et al., 2012). The clinical grade of the infections however differed, with subcutaneous inoculations often resulting in milder signs than intranasal or intravenous administration, accompanied with a slight delay in signs (Harrak et al., 2012). The similarities in the signs induced by different inoculation routes suggest that, as for other *Morbillivirus*, PPRV dissemination is probably systemic. Typically in experimental infections, clinical signs start to appear by day 4-5, peak by day 7-8, and eventually subside by day 10-11 when the infected animals start mounting an effective immune response. The kinetic of infection is probably slower in natural infections as the initial viral dose is low.

In most studies, experimental infections result in milder clinical signs than those observed naturally (Pope et al., 2013; Truong et al., 2014), although some studies have reported mortality rates up to 100% in subcutaneously infected goats (Couacy-Hymann et al., 2007; Kumar et al., 2004). Discrepancies in clinical signs between experimental studies are likely due to differences in virulence of the used PPRV strains, in host animals selected (goats are more susceptible than sheep), as well as in the health status of the animal at the start of the experiments. Concurrent parasitic or bacterial infections are likely to worsen clinical signs due to PPRV immunosuppressive effects (Emikpe et al., 2010; Malik et al., 2011). A major consideration for data interpretation in experimental infections should thus be that although other routes produce at least similar clinical signs, intranasal inoculation is likely to better recapitulate the natural pattern of infection.

PPRV Dissemination

Histological analysis of intranasal experimental infections with virulent PPRV strains have shown an initial site for virus replication in the tonsilar tissue and lymph nodes draining the inoculation site (Pope et al., 2013). Virus is then detected in distant lymphoid organs (Peyer's patch, distant lymph nodes, spleen) pointing at a systemic dissemination (Truong et al., 2014). Finally viral antigens, N and H are detected by

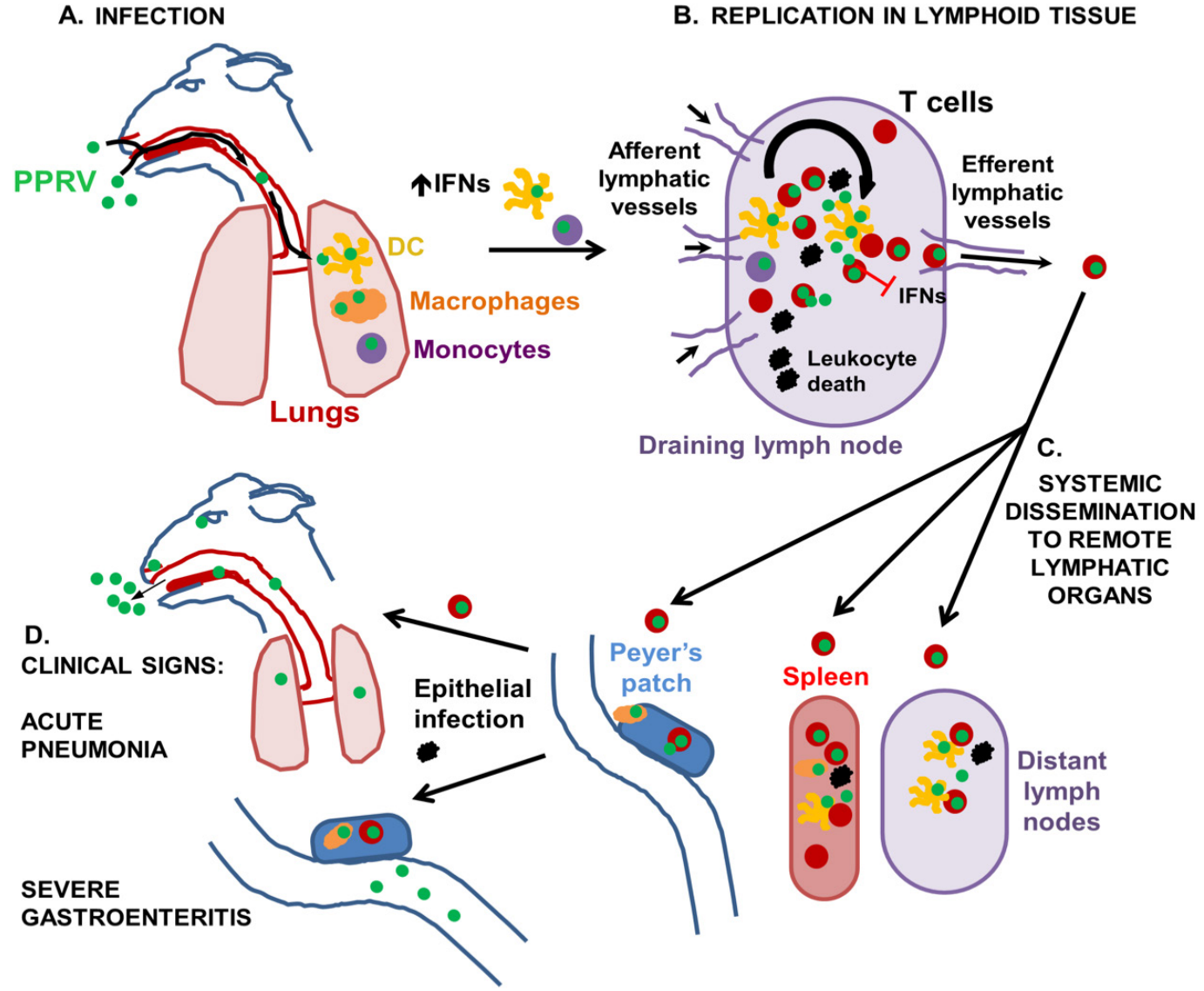

Figure 1: *PPRV infection model:* **A)** *PPRV infection occurs through the respiratory tract, where antigen presenting cells (APC) (possibly dendritic cells (DC), macrophages and monocytes) are infected. Early infection results in IFN induction probably leading to APC migration to the draining lymph node.* **B)** *Once infected APC reach the draining lymphatic organ, where PPRV further replicates, causing cell death. PPRV blockade of IFN response and signaling helps the virus immunosuppress the host and spreading.* **C)** *PPRV is then disseminated systemically (probably through T cells) to distant lymphatic tissue where further replication and virus expansion can occur.* **D)** *Finally, PPRV infects epithelia, where more evident clinical signs of infection are detected (pneumonia and gastroenteritis) and high viral loads can be detected. It should be noted that virus shedding starts prior to severe clinical signs appear.*

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immunohistochemical staining in most lymphoid organs, facial epithelia and gastrointestinal tract (Kumar et al., 2004; Parida et al., 2015; Pope et al., 2013; Truong et al., 2014) (Figure 1). This course of infection is very similar to aerosol MeV-infected macaques where early replication occurs in lung, where MeV infects antigen presenting cells (DC/macrophages/monocytes), which then migrate to draining lymphatic organs where further infection occur and systemic dissemination takes places (de Vries et al., 2010a; Ferreira et al., 2010; Lemon et al., 2011). There is histological evidence showing the existence of $CD68^+$ (a monocyte/macrophage marker) syncitia in PPRV-infected lungs (Truong et al., 2014), which suggests that PPRV is likely to also target antigen presenting cells. Histological analysis at day 2 and 5 of goats inoculated intranasally with virulent PPRV showed no evidence of viral antigens in oral epithelia, confirming that epithelial infection occurs at a later stage, probably after systemic dissemination. Infection of the gastrointestinal tract also appears to take place after systemic dissemination in these experiments. The systemic route of dissemination is also confirmed by the observation that day 5 peripheral blood leucocytes tested positive for PPRV by RT-qPCR (Pope et al., 2013). It should be nonetheless noted that although epithelial PPRV infection occurs at a late stage, PPRV shedding could still take place before clinical signs fully appear, as exemplified by the detection of viral RNA in ocular and nasal swabs in day 3 samples (Couacy-Hymann et al., 2009; Hammouchi et al., 2012; Pope et al., 2013).

Evidence is mounting that PPRV uses cells of the immune system in the respiratory tract to initiate its replication and subsequently further infects immune cells in the draining lymphatic organs to facilitate its systemic dissemination in the host (Figure 1). Eventually, the virus reached the oral and intestinal epithelium where the more severe and observable signs are detected.

PPRV and Leucopenia

As a member of the Morbillivirus genus, PPRV bases its successful infection on targeting leucocytes. This lymphotropism causes severe leucopenia and lymphopenia during the acute phase of the disease in goats and sheep (Rajak et al., 2005; Rojas et al., 2014). Total white blood cell counts usually decrease by more than 25% during the acute phase of infection (Baron et al., 2014; Herbert et al., 2014; Pope et al., 2013; Rajak et al., 2005; Rojas et al., 2014). PPRV induces apoptosis in peripheral blood mononuclear cells *in vitro* (Mondal et al., 2001), and extensive necrotic lesions can be detected in spleen, lymph nodes, thymus and Peyer's patches (Kul et al., 2007; Kumar et al., 2004; Pope et al., 2013). PPRV cytopathogenic effects could thus account for the leucocyte depletion.

A significant decline in both $CD4^+$ and $CD8^+$ T-cells was observed by day 3 after challenge with a virulent PPRV strain (Rojas et al., 2014). Moreover, T-cell responsiveness to mitogen stimulation was significantly reduced by PPRV in sheep and goats (Heaney et al., 2002; Liu et al., 2008; Rojas et al., 2014). These studies indicate that PPRV infection not only depletes T cells, it also impairs T cell activation. It is noteworthy that leucopenia and partial immunosuppression is observed in animals vaccinated with an attenuated live PPRV vaccine while this is not detected in vector based vaccine immunized animals (Herbert et al., 2014; Rajak et al., 2005; Rojas et al., 2014). Concomitantly with infection, a significant increase in B cells was observed, suggesting a T-cell-independent B-cell activation response (Herbert et al., 2014; Rojas et al., 2014). Seven days post-challenge, Herbert et al. (2014) detect a slight increase in the percentage of $CD8^+$ T-cells in both unvaccinated and vaccinated goats, and Rojas et al. (2014) detect an increase in $CD4^+$ T-cells in unvaccinated sheep, suggesting induction of T cell responses by PPRV infection at this stage.

Because of the lymphotropism and immunosuppressive effects induced by PPRV (Herbert et al., 2014; Rajak et al., 2005; Rojas et al., 2014), T cell responses are likely to be delayed, providing the virus with a window of opportunity where it can replicate and spread. T cell responses are eventually mounted in unvaccinated animals after challenge as indicated by the increased production of PPRV specific IgG (Rojas et al., 2014), which requires T-cell help for class switching (Fazilleau et al., 2009).

Other mechanisms of cellular inhibition may also come into play. For instance, in the Morbillivirus prototype MeV, the N protein can suppress T cell proliferation when released by epithelial cells (Laine et al., 2003). MeV-N protein can also block antibody production (Ravanel et al., 1997) and thus further contribute to lymphocyte immunosuppression. Whether PPRV uses similar approaches as MeV will require further work. These studies highlight the profound immunosuppressive effects that PPRV has on lym-

phocytes during the acute phase of infection. This can lead in some cases to the host death probably due to secondary infections that take advantage of the suppressed immune system.

Cytokine Expression Profile during Infection

PPRV infection produces an increase in the expression of a classical pro-inflammatory cytokines IL-1β, IL-6, IL-8, IL-12, IFNβ and IFNγ, (Atmaca and Kul, 2012; Baron et al., 2014; Patel et al., 2012; Truong et al., 2014). RNA levels of IFN-β and IFN-γ appears rapidly after infection, however their levels decrease by day 6 (Baron et al., 2014). The RNA levels of other pro-inflammatory cytokines (IL-1β, IL-6, IL-8) do not appear to be altered at later stages of infections. Eventually, IFN-β production recovers probably coinciding with the generation of the adaptive immune response (Patel et al., 2012; Truong et al., 2014). It could be speculated that early IFNs production is probably necessary to trigger the activation and migration of infected antigen-presenting cells from the lung to the draining lymphatic tissue. Once the virus arrives in the lymphoid tissue, it can rapidly replicate and induce an adequate IFN blockade resulting in the decreased IFN levels detected in blood by Baron et al (Baron et al., 2014).

The expression of pro-inflammatory cytokines is also accompanied by an early induction of T helper 2 cytokine IL-4, which is likely to promote anti-PPRV B cell responses (Baron et al., 2014; Patel et al., 2012). IL-4 expression is nonetheless transient in blood and decreases by day 6 (Baron et al., 2014). Whether this is due to PPRV immunosuppressive effects remain to be determined. Baron et al have also described an early induction of the immunomodulatory cytokine IL-10 following PPRV infection. IL-10 induction correlated with a decrease in IL-12A transcripts, which encode for the subunit specific for the inflammatory cytokine IL-12 (Baron et al., 2014). IL-10 is a key regulator of inflammatory and T helper 2 responses, whose role is essential for infection resolution (Couper et al., 2008; Filippi and Herrath, 2008). Early expression of IL-10 in PPRV-infected animals could thus play a role in PPRV pathogenesis and inhibit early inflammatory responses in order to delay adaptive immunity. IL-10 detection nonetheless occurs in infected goats independently of the strain virulence, and could thus also be part of a normal anti-PPRV immune response. Indeed, IL-10 is induced in goat PBMC along with classical pro-inflammatory cytokines (Dhanasekaran et al., 2014). Further work on cytokine profiling during infection is therefore necessary to shed more light on the contribution of these factors to immunosuppression.

PPRV Interaction with the Immune System

Innate immune response: PPRV has two natural host receptors: the signalling lymphocyte activation molecule (SLAM) protein, exclusively expressed in immune cells and Nectin-4 present in epithelium (Birch et al., 2013). PPRV infect the host through the respiratory tract, where its interaction with SLAM makes possible the infection of mucosal lymphocytes, macrophages and dendritic cells (Pawar et al., 2008; Pope et al., 2013), leading to its transport to the lymph nodes for multiplication and spread. The Morbillivirus H protein interacts with the cell receptor(s) that allow viral attachment to cells, thus representing the first contact point between virus and host cell. H protein properties vary between viruses, *e.g.* H from PPRV or MeV agglutinate red blood cells, whereas H from RPV does not (Langedijk et al., 1997; Lecouturier et al., 1996; Scheid and Choppin, 1974a, b; Seth and Shaila, 2001). The H protein from MeV interacts with TLR2 and induces SLAM expression in monocytes (Bieback et al., 2002). This increased expression of SLAM could in turn favour further infection leading to increased viral replication and spreading.

The interaction of PPRV H protein with host cells could thus be part of the different pathogen associated molecular patterns (PAMPs) such as dsRNA, CpG DNA and uncapped ssRNA with 5' triphosphate that are generated by RNA viruses (Akira et al., 2006; Medzhitov, 2007) and can be recognized by pattern recognition receptors (PRRs). Viral components are mainly detected by three types of PRRs (Kawai and Akira, 2010; Takeuchi and Akira, 2009): Toll-like receptors (TLRs), 3/7/8 (Finberg and Kurt-Jones, 2004; Finberg et al., 2007), melanoma differentiation associated factor 5 (MDA-5) and retinoic acid-inducible gene-I (RIG-I) like receptors (RLRs) (Kato et al., 2006), and nucleotide oligomerisation domain-like receptors (NLRs) (Ichinohe et al., 2009). The innate immune system acts first through these mechanisms to establish an antiviral state in the host (Platanias, 2005; Randall and Goodbourn, 2008).

Studies addressing the immunological correlation between PPRV and TLRs start to appear and to become relevant in the landscape of PPRV immuno-

suppression. TLRs play a key role in innate immunity initiating a complex signalling cascade that activates different inflammatory cytokines and transcription factors (Takeda and Akira, 2003). TLRs engagement also lead the activation of apoptosis, phagocytosis, complement and pro-inflammatory mediators, essential for the initiation of T-cell mediated immunity (Janeway et al., 1997; Janeway and Medzhitov, 2002; Pasare and Medzhitov, 2004; West et al., 2006). In 2006, the bovine and ovine tissue pattern expression of TLRs 1-10 were elucidated (Menzies and Ingham, 2006), followed by the caprine profile in 2010 (Raja et al., 2011). These patterns are useful tools to correlate TLR expression in different cells and tissues with virulence or susceptibility to a pathogen. Dhanasekaran et al. (2014) describe that high levels of TLR3 and TLR7 and their signal transducers correlates with increased inflammatory cytokine expression and reduced immunomodulatory cytokines favouring the antiviral host state during PPRV infection in four Indian goat breeds and in water buffaloes. TLR3 is expressed in the jejunum or ovine gut epithelium (Menzies and Ingham, 2006) and detects the dsRNA present at some stage in almost all viral infections, whereas immune cells like plasmacytoid dendritic cells express TLR7, a receptor involved in type I IFNs production in response to viral ssRNA. Although, there was no TLR7 nucleotide differences between breeds to which PPRV susceptibility could be attributed, the TLR3 and 7 still appear to play a critical role in PPRV recognition during infection. These differences in viral susceptibility could also be due to polymorphisms in leucine rich repeats domains in the toll-interleukin 1 receptor domain from TLRs (Chang et al., 2009; Raja et al., 2011).

Protective immune response: Different researchers have demonstrated that PPRV infection induces strong virus-specific humoral and cellular immune responses resulting in lifelong immunity (Cosby et al. 2006). Humoral and cellular responses against the virus are mainly directed against the two PPRV glycoproteins (F and H) and the N protein (Sinnathamby et al., 2001). Immunisation with F and/or H induces protective humoral immunity probably through the production of neutralizing antibodies, whilst the antibodies generated with the N protein immunisation are not neutralizing (Diallo et al., 2007; Rojas et al., 2014). However, a strong cellular immune response was developed to N, which is thought to correlate with protection (Sinnathamby et al., 2001). Strategies allowing the expression of PPRV F and/or H proteins using different vectors, including recombinant poxviral (Berhe et al., 2003; Chen et al., 2010), adenoviral (Herbert et al., 2014; Liu et al., 2008; Qin et al., 2012; Rojas et al., 2014) or chimeric RPV vectors (Das et al., 2000; Taylor, 1979) can induce long lasting neutralizing antibody responses against PPRV in goats or sheep as well as partial or total protection against the disease.

As in MeV infection, virus neutralizing antibodies are an important correlate of protection against PPRV infection. Although, a study on RPV did not correlate neutralizing antibodies with protection (Bassiri et al., 1993), suggesting that protection was not solely due to the antibody responses. Indeed, the resolution of Morbillivirus prototype MeV infection correlates with lymphoproliferation (Griffin et al., 1989; Mongkolsapaya et al., 1999) and lymph nodes enlargement (de Vries et al., 2012). Cytotoxic T-lymphocytes are also crucial for clearance of MeV-infected cells (de Vries et al., 2010b; van Binnendijk et al., 1990). Ultimately, MeV replication is efficiently restricted, infected cells cleared by the immune system, and lymphocyte numbers restored to normality.

However, viral RNA persists long after infectious virus is not longer detected (Riddell et al., 2007). The slow clearance of MeV RNA after apparent recovery has been related with the switch of T cell responses from type 1 to type 2 with production of IL-10 and IL-4 cytokines (Yu et al., 2008), similar to results obtained in PPRV infections. The prolonged presence of viral RNA might be relevant to the development of persistent infections, described for MeV, and could explain the immunological abnormalities that often persists for weeks after viral clearance (Auwaerter et al., 1999). Although long-term PPRV immunosuppression has not been studied in animals surviving the infection, it could be inferred from MeV data that after the burst of anti-PPRV adaptive immunity, a second wave of immune response could occur to resolve RNA persistent infection. Studies designed to further dissect the multiple immune mechanisms that PPRV employs will therefore be beneficial for the design of more effective PPR therapy.

Suppression of the interferon response by PPRV: Interferons (IFNs) are the main group of cytokines secreted by host cells in response to PAMP recognition by PRRs. The antiviral state established by

IFNs is one of the most important cellular defence mechanisms against viral infections. Type I IFN (α/β) (IFN-I) bind their universally expressed receptor (IFNARI and IFNARII) and regulate the expression of a large set of genes known as interferon stimulated genes (ISGs) (Sen, 2001), such as 2', 5'- oligoadenylate synthetase (2-5OAS), ds RNA-activated protein kinase (PKR), ISG15 or MxA protein (Fujii, 1994; Honda et al., 2006; Samuel, 1991; Sen and Ransohoff, 1993). The intracellular IFN signal transduction pathway signals through Janus protein kinase (JAK)

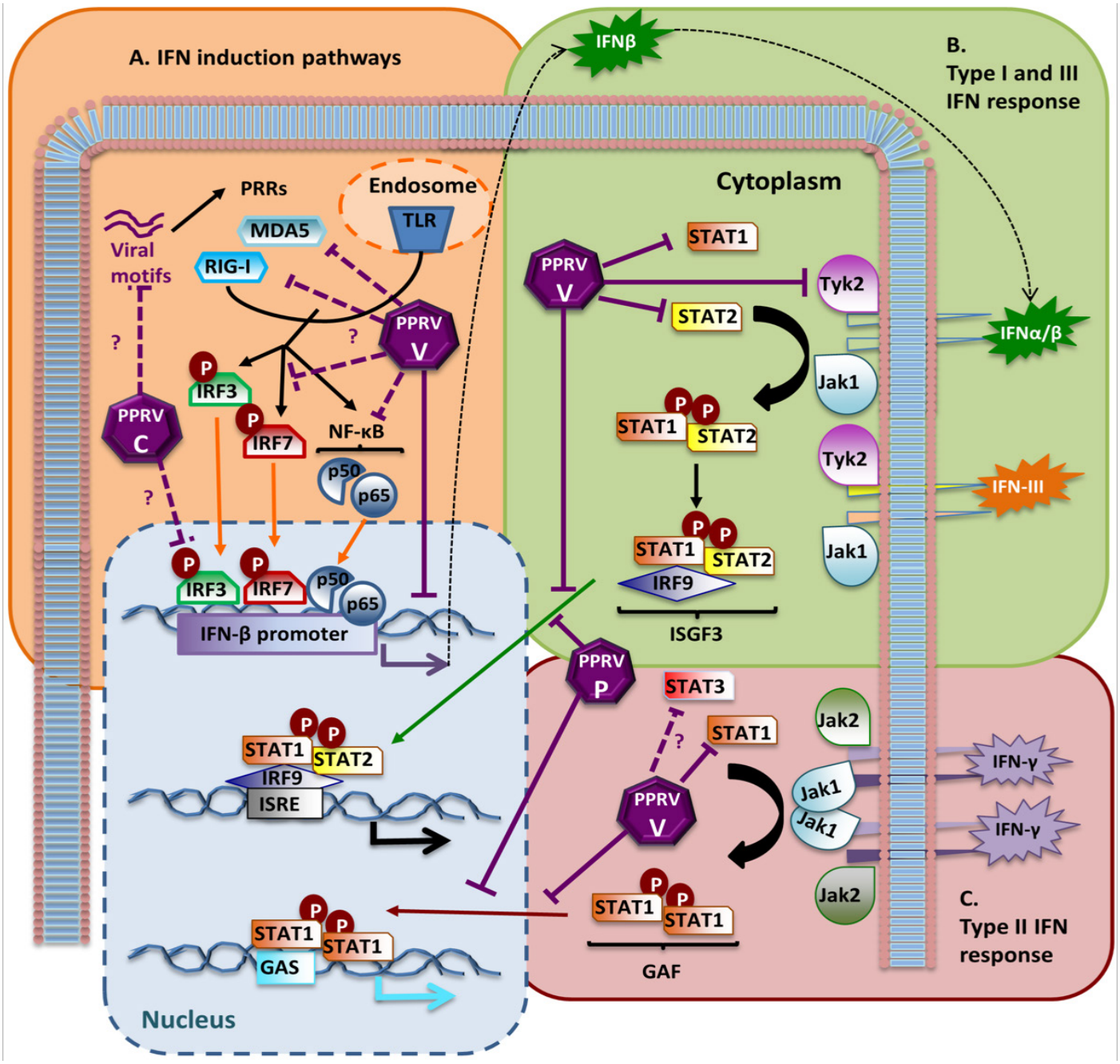

Figure 2: *PPRV-V, -P and -C protein antagonism of IFN induction and response pathways. PPRV-V, -P and C protein can interfere with IFN signaling activity. Full lines indicate blocking effects reported for PPRV proteins, and dotted lines indicate blocking activity for other Morbillivirus proteins.* **A)** *V and C proteins interfere with IFN production. Viral motifs (e.g. double stranded RNA) can be recognized by pattern recognition receptors (PPRs). This leads to IRF3, IRF7 and NF-κB activation, which in turn promotes IFN-β induction. Morbillivirus C protein can impair IRF3 binding to the IFN-β promoter in the nucleus. Morbillivirus C protein can also limit viral replication and consequently limit the amount of viral motifs recognisable for PRRs. PPRV-V protein blocks IFN-β promoter activity, although the mechanism has yet to be elucidated. Morbillivirus V proteins can bind and block RIG-I and MDA5 activity. Morbillivirus V proteins can also suppress NF-κB activity and interacts with IKKα to block IRF7 activation.* **B)** *PPRV-V protein can block Tyk2 phosphorylation and block STAT1 and STAT2 activation, and thus impairs type I and III IFN responses.* **C)** *PPRV-V blockade of STAT1 also antagonizes type II IFN responses. Other Morbilliruses V protein can also block STAT3 activation, which can be involved in type II IFN responses and in transition from innate to adaptive immunity. PPRV-P protein can also inhibit type I and II IFN responses although to a lesser extent than PPRV-V protein.*

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family members that subsequently phosphorylate signal transducer and activator of transcription (STAT) family proteins (Stark et al., 1998). The IFNARI transduces the signal through Jak1 and Tyk2 that in turn phosphorylate STAT1 and 2 triggering their heterodimerization via SH2-phosphotyrosine interactions. The phosphorylated STAT1/STAT2 dimer then associates with interferon regulatory factor 9 (IRF9) to form the transcriptional factor complex ISGF3 that binds IFN-responsive promoter elements (ISRE) into the nucleus and directs ISG expression. The IFN-γ receptor (IFNARII) signals through Jak1 and Jak2 leading to STAT1 phosphorylation and its homodimerization. This homodimer, also called GAF, binds to the IFN-γ-responsive element, called the γ activation sequence (GAS) and drives ISG expression (Goodbourn et al., 2000; Levy et al., 1989; Sen and Ransohoff, 1993) (Figure 2).

Viruses have evolved molecular mechanisms to suppress this antiviral host state to establish infections (Fujii, 1994; García-Sastre, 2001; Goodbourn et al., 2000) by interfering with the IFN induction pathway activated by PAMPs-PRRs and/or with the IFN transducer signal route. Viruses belonging to the Paramyxoviridae family harnessed several strategies to block at different levels the IFN-I signal transduction pathways, such as: (i) suppression of the IFN induction by inhibiting STAT and JAK phosphorylation, used by Sendai virus or human parainfluenza virus type 3 belonging to the Respirovirus genus (Gao et al., 2001; Garcin et al., 1999; Huang et al., 2014; Ikegame et al., 2010; Kato et al., 2001; Komatsu et al., 2004, 2000; Ning et al., 2014), (ii) inactivation of IFN-induced antiviral proteins employed by viruses from the Henipavirus genus (Metz et al., 2012; Zhao et al., 2013), and (iii) interference with IFN signal transduction by modification of the constitutive or basal levels of molecules involved in the JAK/STAT pathway that members of the Rubulavirus genus, like Simian virus 5, mumps virus or human parainfluenza virus type 2, utilize (Chinnakannan et al., 2013; Devaux et al., 2007; Didcock et al., 1999; Fujii et al., 1999; Kubota et al., 2001; Nakatsu et al., 2008; Ramachandran et al., 2008; Sun et al., 2004; Yokosawa et al., 1998).

Next, the role of different PPRV proteins involved in some of these immune system evasion mechanisms are detailed, schematized and summarized in Figure 2.

P Protein

The P gene of Paramyxovirus can encode for up to 6 genes, which can be accessed by a variety of mechanisms (Audsley and Moseley, 2013). The products of these genes are often involved in the suppression of IFN signalling and production. In Morbillivirus, the P gene can potentially encode for 4 proteins: P, V, W and C. The P protein is essential for viral RNA synthesis and acts as a polymerase cofactor. In MeV, it can also impair STAT1 phosphorylation and block its translocation to the nucleus (Devaux et al., 2007), thereby limiting IFN-I and II signalling. Similarly, RPV-P protein can block STAT1 phosphorylation and impair IFN signalling (Nanda and Baron, 2006). In PPRV, the P protein also reduces the ISRE and GAS promoter activity, but little to no inhibition of the IFN-β promoter activity was observed (Ma et al., 2015). It should be noted nonetheless that the P protein contribution to IFN signalling and production blockade is probably less critical than that of V (Nanda and Baron, 2006), another product of the P cistron.

V Protein

The different strategies for IFN signalling evasion are orchestrated in the Paramyxovirus mainly by the virus-encoded V protein, present in the Respirovirus, Henipavirus, Rubulavirus and Morbillivirus genera. This viral protein with a molecular weight ranging from 28-32 KDa, is phosphorylated and binds N and L proteins (Sweetman et al., 2001). The V protein, and the W protein only described for some of these genera, are produced by an unusual editing strategy consisting in a frame shift in the open reading frame for the P cistron, due to the insertion of 1 (G) or two (GG) guanine/s at the conserved RNA editing site 5'-TTAAAAGGGCACAG-3', leading to the production of V or W protein respectively; with no insertion at the site resulting in P protein synthesis (Mahapatra et al., 2003). The PPRV-V protein presents an amino-terminal domain, common to the viral P, V and W proteins but not highly conserved among Paramyxovirus, and a carboxy-terminal domain containing a zinc finger structure consisting in a histidine and a cysteine-rich V-specific domain, which is conserved among all them (Liston and Briedis, 1994; Paterson et al., 1995).

Recent studies have demonstrated that the Morbillivirus V proteins interfere with different steps in the IFN-I transduction pathway, blocking the IFN signalling and contributing to the inhibition of the cellular antiviral state. There is a notable diversity in the

mechanisms used by Paramyxovirus genera that even vary between members of the same genus.

wild strains of the Morbillivirus genus prototype, MeV, display nearly complete suppression of IFN-α induced antiviral state, but not IFN-γ induced state. The MeV-V protein interacts via its amino-terminal domain with Jak1 and inhibits STAT-1 and STAT-2 phosphorylation, thereby preventing their dimerization and nuclear import, and thus impairing signal transduction (Caignard et al., 2009, 2007; Chinnakannan et al., 2013; Fujii et al., 1990, 1988; Ramachandran et al., 2008; Yokota et al., 2003). Similar interactions between the V proteins from other Morbillivirus (CDV, RPV) and STAT1 are also described (Nanda and Baron, 2006; Rodriguez et al., 2004). Moreover, a zinc finger domain and specific residues in the carboxy-terminal domain of the MeV-V protein are involved in the association with STAT2 (Ramachandran et al., 2008).

PPRV shares some of the immune system evasion mechanisms with other members of the same genus, like MeV or RPV. In the closely related-RPV, the amino-terminal domain in the V protein binds STAT1, whereas the carboxy-terminal domain interacts with the IFN receptor-associated kinases Jak1 and Tyk2. Like for the Morbillivirus prototype MeV, both RPV amino- and carboxy- V domains were necessary to block the IFN-induced antiviral state (Chinnakannan et al., 2014). Likewise, the PPRV-V protein contributes to innate immune evasion by blocking IFN-I signalling pathway through its interaction with STAT1 and STAT2. As for MeV, the amino-terminal and carboxy-terminal V domains, bind STAT1 and STAT2, respectively, disturbing their distribution and nuclear translocation but not inducing their degradation. PPRV-V protein produces stronger inhibition of the ISRE and GAS promoter expression than N and P proteins (Ma et al., 2015). The mutation of the Tyr-110 residue to Ala in the PPRV-V amino-terminal domain impaired its ability to inhibit IFN signalling, supporting this domain role in antagonising the IFN transduction pathways (Ma et al., 2015). The conserved Cys cluster and the Trp motif in the zinc finger structure in the carboxy-terminal domain of PPRV-V protein are implicated in the STAT2 interaction, with two amino acids (275 and 277) critical for this route blockade (Ma et al., 2015). PPRV-V thus allows the virus to suppress both IFN signalling pathways.

The virulence factor V from Morbillivirus not only acts on STAT1 and STAT2, it can also interfere upstream of these factors and inhibits the phosphorylation of Jak family members. The V protein from MeV, CDV, RPV and PPRV can inhibit Tyk2 phosphorylation, whereas only the V protein from a virulent RPV strain could impair Jak1 phosphorylation (Chinnakannan et al, 2013). In these experiments, all V proteins co-immunoprecipitated both Jak1 and Tyk2 independently of their effect on phosphorylation. This indicates that the V protein probably binds the Jak1/Tyk2 complex at the IFNAR receptor, which in turn could impair signal transduction. This complementary IFN-I signalling inhibitory mechanism illustrates the diverse routes that Morbillivirus can employ to block IFN-I and –II signalling, and highlights the importance of this pathway in the pathogenicity of this genus.

Fewer studies have looked at PPRV-V inhibition (or closely-related RPV) of the IFN production route or its interaction with RIG-I-like receptors (RLR). The V proteins tested in at least 13 Paramyxovirus bind to MDA5 inhibiting IFN induction (Childs et al., 2007; Parisien et al., 2009; Ramachandran and Horvath, 2010). The carboxy-terminal domain from the MeV-V protein has been implicated in MDA-5 binding. This domain from MeV-V can also interact with the laboratory of genetics and physiology 2 protein (LGP2), instead of directly with RIG-I to inhibit its signal transduction (Childs et al., 2012; Parisien et al., 2009). MeV-V can also interfere with signalling pathways induced by other PRRs. MeV-V can inhibit IFN production induced by TLR7/9 in plasmacytoid DC (Pfaller and Conzelmann, 2008; Schlender et al., 2005). MeV-V protein interacts with IKKα preventing IRF7 activation and thus IFN-β production. MeV-V (and to a lesser extent the P protein) can also suppress NF-κB activity (Schuhmann et al., 2011). Although, the interaction of RPV- or PPRV-V proteins with RLR or TLR transduction pathway members have not been explored, it appears that RPV inhibits MDA-5 signalling through the C protein rather than with the V protein (Boxer et al., 2009). PPRV-V can nonetheless inhibit the IFN-β promoter activity (Ma et al., 2015), which indicates that RPV-V and PPRV-V function do not fully overlap. Whether PPRV-V uses similar targets as MeV-V to block PRR transduction signals remains to be determined. Similarly to other V proteins in Morbillivirus, the PPRV-V protein plays an essential role in inhibiting the antiviral cellular response by impairing IFN-I and –II signalling and but also by blocking IFN produc-

tion.

Although, STAT1 and STAT2 inhibition by Morbillivirus V proteins have been extensively studied, the Morbillivirus V could also target other antiviral signalling routes. MeV-V can also interact with STAT3 and target it for proteasomal degradation (Palosaari et al., 2003). Interference with STAT3 is also described in mumps virus, another Paramyxovirus (Ulane et al., 2003). The role of STAT3 is complex since it can be activated by multiple cytokines and regulates genes with opposite effects (Kuchipudi, 2015). Since Paramyxovirus target STAT3 for degradation, it appears that this virus family benefit from STAT3 inhibition. STAT3 activity is important in adaptive immunity, particularly in T cell survival and proliferation (Durant et al., 2010; Oh et al., 2011; Takeda et al., 1998; Yu et al., 2013). STAT3 is also the main transducer of IL-6 signalling, which is a key component of the transition from innate to adaptive immunity (Jones, 2005). It could thus be speculated that inhibition of T cell responses via STAT3 degradation by V proteins could extend the window for virus replication before an adequate adaptive immune response is mounted. Moreover, activated STAT3 can bind GAS to promote IFN-II-regulated gene expression (Darnell et al., 1994; Timofeeva et al., 2012). Whether V proteins target this route to complement GAS inhibition or to favour other pathogenic effects remains to be determined. Although viral inhibition of this route has not been widely studied, in part probably due to its complexity, the observation that MeV targets this pathway is likely to contribute to immunosuppression. Given that most Morbillivirus V proteins have similar signalling targets, it would be relevant to determine whether PPRV-V also uses STAT3 degradation to evade immunity.

W Protein

Little is known about the role of Morbillivirus W protein in immunosuppression. In MeV, W transcripts account for only 5% of total transcripts from the P cistron, but no evidence of W protein expression in this virus was obtained (Bankamp et al., 2008). Sequence analysis in PPRV reveals that PPRV-W has a longer C-terminal tail (11 amino-acids) than MeV (5-10 amino-acids) or RPV (3 amino-acids), which could give these proteins properties other than those of a "truncated" P or V protein (unpublished data from our laboratory). In RPV, W binds STAT1 (Nanda and Baron, 2006) and inhibits both ISRE and GAS promoter activity in reporter assays (Chinnakannan et al., 2014). The presence in W and P proteins of an amino-terminal domain similar to V indicates that these proteins share the ability to bind STAT1, probably through the conserved domain proximal to Tyr110 (Chinnakannan et al., 2014; Devaux et al., 2007). RPV-W can also inhibit Tyk2 phosphorylation (Chinnakannan et al., 2014, 2013), but unlike RPV-V does not bind STAT2, indicating that W and V only share some IFN-signalling inhibitory features. Further work needs to be done to thoroughly assess Morbillivirus W protein expression, and to determine the relevance of PPRV-W in inhibiting the antiviral cellular state.

C Protein

PPRV genome, as all the Paramyxovirus, encodes for the C protein, another non-structural virulence factor expressed from an alternate open reading frame, from a second ATG codon embedded in the first half of the P cistron (Bellini et al., 1985; Cattaneo et al., 1989; Devaux et al., 2007; Yamaguchi et al., 2014). This protein has a predicted molecular weight of 20 KDa, is not phosphorylated, binds to the L protein and, is localized in the nucleus and cytoplasm (Bellini et al., 1985; Sweetman et al., 2001). The C protein has different roles in immune evasion and pathogenicity (Gotoh et al., 2001; Horvath, 2004; Patterson et al., 2000). In Morbillivirus, C is usually associated with the inhibition of IFN production through two main mechanisms: firstly, C protein reduces viral replication, thereby decreasing the amount of motifs that PRRs can recognize and consequently limiting IFN production (Bankamp et al., 2005; Nakatsu et al., 2008, 2006); and secondly, C proteins directly interfere with the PRRs signalling that leads to IFN transcription (Boxer et al., 2009; Schuhmann et al., 2011; Sparrer et al., 2012).

MeV-C and RPV-C targets in PRRs signalling have been identified, but, to the best of our knowledge, PPRV-C has not been studied. MeV-C and RPV-C target IRF3 in the nucleus and block the induction of IFN-I, although the exact mechanism of action is unknown (Boxer et al., 2009; Sparrer et al., 2012). The C protein interferes with IRF3-dependent transcription without affecting IRF3 phosphorylation, dimerization or nuclear accumulation (Sparrer et al., 2012), and thus its mechanism of action could rely on a steric hindrance of IRF3 dimers with the IFN-β promoter. MeV-C can also block NF–κB signalling, though to

a lesser extent than V, suggesting that Morbillivirus C proteins may still use other mechanisms to suppress host immune responses (Schuhmann et al., 2011). MeV-C is also reported to block IFN-I signalling (Shaffer et al., 2003), although the V protein is probably the main IFN signalling antagonist during infection (Nakatsu et al., 2008). Overall, the Morbillivirus C protein suppresses the IFN induction pathways, an essential component in the initiation of the innate immune response. To further our understanding of PPRV immunosuppressive mechanisms, it will thus be of great significance to assess if, as predicted, PPRV-C behaves like its MeV and RPV counterparts and/or if it affects other members of the PRRs pathways.

Non-Coding RNA, Pathogenicity and Immune Evasion

Non-coding RNA segments are involved in immune modulation in some viruses (Kincaid and Sullivan, 2012). Morbillivirus have long untranslated regions (UTR) that regulate M and F gene expression. In MeV, the long M 3' UTR promotes M protein production and virus replication, whereas the long F 5' UTR reduces F protein production and thus cytopathogenicity. It could be speculated that reduced cytopathogenicity would reduce virus exposure to the immune system and thus favour immune evasion (Wohlsein and Saliki, 2006). Indeed, cell-cell fusion induced by MeV can increase IFN-I response and thus antiviral immunity (Herschke et al., 2007). In CDV, a similar control of F and M expression is described (Anderson and Messling, 2008). Short M 3' UTR in CDV has also been linked to attenuation of experimental infection and a reduction in immunosuppression (Anderson et al., 2012; Rudd et al., 2006). The immunosuppressive effects of these UTR could be due to a combination of several processes e.g. reduced recognition of these long UTRs by PRRs, presence of small RNA species in these regions capable of interfering with the pathogen recognition processes, and/or indirect effects derived from reduced pathogen exposure to the immune system. Overall, these regions appear to be important for Morbillivirus virulence. PPRV also possesses these long M 3' UTR and F 5' UTR that can potentially contribute to immunosuppression (Haffar et al., 1999; Meyer and Diallo, 1995); although further work will be necessary to assess the role of these non-translated regions in PPRV immune evasion and suppression.

Conclusions

The multitude of mechanisms that the Morbillivirus genus employs to impair immune response turns out to be the seal of the diseases they cause. These mechanisms lead to the hallmark immunosuppression generated in hosts, increasing the susceptibility to opportunistic infections that often are the agents causing mortality (Wohlsein and Saliki, 2006).

The immunosuppression features triggered by Morbillivirus, and PPRV among them, are closely related to the damage in lymphoid organs detected. The leucopenia detected in PPRV infections could be attributed to extensive necrosis in spleen, thymus, pulmonary lymph nodes and Peyer's patches (Kul et al., 2007; Kumar et al., 2004; Pope et al., 2013) and to PBMCs apoptosis as showed in vitro (Mondal et al., 2001). Aside from this direct infection and consequent destruction of lymphoid cells, it is clear that the IFN route is affected and modulated through different mechanisms by PPRV. Different viral proteins are implicated in this process, from viral attachment glycoproteins, such as H, that interact with cell receptors and could promote infection, to non-structural proteins like C or V that interact directly or indirectly with different members of the IFN transduction and production pathways. PPRV, like most of the Paramyxovirus has multiple strategies to overcome the host interferon-mediated innate immune response through the activity of his principal IFN antagonist protein, V. Although there is a remarkable IFN inhibition mechanism diversity between different genera of this viral family, such as inhibition of phosphorylation, proteasome degradation and subcellular miss-localization, the common targets of the IFN system, are the following molecules: MDA-5, RIG-I, STAT1, STAT2 and IRF3. At present, the inhibition of IFN signalling by PPRV is documented by its interaction and subsequent miss-localization of STAT1 and 2. TLR3 and 7 have been proposed as possible PPRV targets due to the interrelationship between TLR3/TLR7 amounts and PPRV susceptibility.

The immunosuppression provoked by PPRV is an intricate and multifactorial process. A deeper and more accurate understanding of the mechanisms by which PPRV immunosuppresses its hosts is needed and will allow the development of more effective, targeted and successful treatment of the disease. Opportunistic infections could progress during the delay in the immune response observed after PPRV infection but also after vaccination with attenuated live vaccines.

This drawback produced by current live attenuated vaccines could be overcome with vaccines based on recombinant vectors or protein expression.

In the last years substantial progress has been made in the identification of viral factors involved in the host immunosuppression, although future studies using *in vivo* infection models are needed to clearly understand the mechanisms employed by these viruses, in particular PPRV, to interact with the host immune system.

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