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Review article

Antagonizing cytokine-mediated JAK-STAT signaling by porcine reproductive and respiratory syndrome virus

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ABSTRACT

Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway is activated by myriad cytokines, which are involved in regulation of cell growth, proliferation, differentiation, apoptosis, angiogenesis, immunity and inflammatory response. Because of its significance in immune response, JAK-STAT pathway is often targeted by pathogens, including porcine reproductive and respiratory syndrome virus (PRRSV). PRRSV causes reproductive failure in sows and respiratory disease in pigs of all ages. A typical feature of the immune response to PRRSV infection in pigs is delayed production and low titer of virus neutralizing antibodies, and weak cell-mediated immune response. One of the possible reasons for the weak protective immune response is that PRRSV interferes with cytokine-mediated JAK-STAT signaling. PRRSV inhibits interferon-activated JAK-STAT signaling by blocking nuclear translocation of STAT1 and STAT2. The mechanism is that PRRSV non-structural protein 1β (nsp1β) induces degradation of karyopherin α1 (KPNA1), a critical adaptor in nucleo-cytoplasmic transport. PRRSV also antagonizes IL6-activated JAK-STAT3 signaling via inducing degradation of STAT3. In this review, we briefly introduce JAK-STAT signaling, summarize the PRRSV interference with it, and provide perspective on the perturbation in the context of PRRSV-elicited immune response.

Contents

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1. Introduction

Cytokines are a broad and loose group of small cell-signaling proteins that play important roles in cell growth, proliferation, differentiation, apoptosis, angiogenesis, immunity and inflammatory response. They include interferons (IFN), interleukins (IL), chemokines, lymphokines, and tumor necrosis factors (TNF). They are produced by a variety of cells, including macrophages, B and T lymphocytes, mast cells, endothelial cells, epithelial cells, fibroblasts, and various stromal cells. Cytokines that are produced at the site of infection stimulate and coordinate innate and adaptive immune responses against invading pathogens (Gonzalez-Navajas et al., 2012; Iwasaki and Medzhitov, 2015; Takaoka and Yanai, 2006). They act through their matching receptors on the surface of target cells, followed by cascades of intracellular signaling. One such frequently activated intracellular signaling is the JAK-STAT pathway, which is indispensable and pivotal in many biological processes including immunity and inflammatory response (O'Shea et al., 2015; Stark and Darnell, 2012). Dysregulation of JAK-STAT signaling results in immunodeficiency and immune-mediated disorders (O'Shea and Plenge, 2012; O'Shea et al., 2015). Mutations in the components of JAK-STAT pathway cause immunodeficient and autoimmune disorders (Casanova et al., 2012; Kane et al., 2014). Due to the importance of JAK-STAT signaling in the host immune response, it is often targeted by pathogens, including PRRSV (Patel et al., 2010; Wang et al., 2013a, 2013b).

PRRSV causes a contagious disease that is characterized by reproductive failure in sows and respiratory disease of variable severity in pigs of all ages (Lunney et al., 2016). PRRS has caused substantial economic losses to the swine industry and remains one of the most economically important diseases in pigs since it was first reported in 1987 (Holtkamp et al., 2013; Neumann et al., 2005). A typical feature of the immune response to PRRSV infection in pigs is delayed production and low titer of virus neutralizing antibodies, and weak cell-mediated immune response (Labarque et al., 2000; Lunney et al., 2016; Xiao et al., 2004). PRRSV infection is also characterized by prolonged viremia followed by the persistent presence in regional lymph nodes for as long as 250 days (Wills et al., 2003). One of the possible reasons for the weak protective immune response is that PRRSV interferes with innate immunity, including type I interferons (IFNs), and cytokine-mediated JAK-STAT signaling (Albina et al., 1998; Buddaert et al., 1998; Patel et al., 2010; Sun et al., 2012a; Wang et al., 2013b; Wang and Zhang, 2014).

1.1. JAKs and STATs

In mammals, there are four JAKs: JAK1, JAK2, JAK3, and Tyk2, ranging in size from 120 to 140 kDa (Haan et al., 2006). JAK1, JAK2, and Tyk2 are ubiquitously expressed, whereas JAK3 expression is restricted to cells of the hematopoietic system. The JAK protein is pre-associated with cytokine receptors in the cytoplasmic side and is an important determinant of their levels and signaling potential (Haan et al., 2006). Upon cytokine binding, the receptor chains are brought into close proximity, leading to the juxtaposition of two JAK kinase domains and consequent trans-phosphorylation. Once activated, JAKs phosphorylate STAT proteins via Src homology 2 (SH2) domain interaction (Heim et al., 1995). Even though responding to different cytokines, JAKs selected by different receptors activate specific STAT members for defined functions (Haan et al., 2006).

There are seven mammalian STAT proteins: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6, which range from 750 to 950 amino acids in polypeptide length and feature several conserved domains (Schindler, 1999; Stark and Darnell, 2012). STATs are latent transcription factors located in the cytoplasm until activated. Each STAT member responds to a defined set of cytokines (Kuchipudi, 2015; O'Shea and Plenge, 2012; O'Shea et al., 2015). The seven STATs go through similar activation processes and exhibit global conservation in function (Stark and Darnell, 2012). In brief, ligand-mediated receptor multimerization leads to trans-phosphorylation of JAKs, which then create docking sites in the receptor for STATs and phosphorylate them. Phosphorylated STATs form homodimer or heterodimer complexes, followed by translocation into the nucleus by importins and binding to response element in DNA to activate or repress transcription of a defined set of genes (Stark and Darnell, 2012).

1.2. STAT signaling and functions

Among the seven STATs, STAT1 and STAT2 mainly mediate the IFN-activated signaling (O'Shea and Plenge, 2012). STAT1 is involved in signaling by type I, type II, and type III IFNs. In response to type I IFNs (IFN-α or IFN-β), STAT1 and STAT2 are phosphorylated, followed by heterodimer formation and then interaction with interferon regulatory factor 9 (IRF9) to form a heterotrimer known as interferon-stimulated gene factor 3 (ISGF3) (Darnell et al., 1994) (Fig. 1A). The ISGF3 is translocated into nucleus and binds to interferon-stimulated response element (ISRE) in DNA to activate the expression of interferon-stimulated genes (ISGs). Upon IFN-γ stimulation, activated STAT1 forms homodimers, followed by nuclear translocation and activation of gene expression via binding to interferon-gamma-activated-sequence (GAS) in DNA (O'Shea and Plenge, 2012). Type III IFNs also activate STAT1 and STAT2 for ISRE transactivation like type I IFNs (Zhou et al., 2007).

In addition to the canonical signaling described above, IFNα signaling occurs through alternative complexes containing STAT2 and IRF9 without STAT1 (Bluyssen and Levy, 1997; Fink and Grandvaux, 2013) (Fig. 1B). Moreover, STAT2 can form heterodimer with other STATs, like STAT3 and STAT6, followed by binding to diverse sequences, like GAS. Further studies demonstrate the existence of a STAT1-independent IFN signaling pathway, in which STAT2/IRF9 directs a prolonged antiviral activity (Blaszczyk et al., 2015; Bluyssen, 2015).

STAT3 is activated by many cytokines and had multiple functions including differentiation of T helper 17 (Th17) and generation of $CD8^+$ T cell memory response (Chen et al., 2006; O'Shea et al., 2015; Villarino et al., 2015). Numerous cytokines including IL-5, IL-6, IL-9, IL-10, IL-11, IL-12, IL-21, IL-22, IL-27, oncostatin M (OSM), IFN-γ, TNF-α and leukemia inhibitory factor (LIF), trigger STAT3 activation (Garbers et al., 2015; Kuchipudi, 2015). The IL-6 family of cytokines including IL-6, OSM, and LIF bind to the receptor complex containing the common glycoprotein 130 (gp130) and activate STAT3, known as gp130/JAK-STAT3 signaling (Fig. 2). STAT3 is needed for differentiation of follicular T helper and Th1 cells (Ray et al., 2014), as well as activation and maturation of dendritic cells (DCs) (Park et al., 2004). Mutations in STAT3 cause autosomal dominant hyper-IgE syndrome, a rare multisystem primary immunodeficiency characterized by recurrent bacterial infections in skin and lung and with abnormally high levels of IgE (Holland et al., 2007; Minegishi et al., 2007). STAT3 is indispensable for promoting host defense against virus infections. For instance, during Herpes simplex virus-1 (HSV-1) infection, STAT3 promotes the activation of CD8+ T cells response (Yu et al., 2013). It has been shown that gp130-STAT3 signaling is critical for the innate immune response against coxsackievirus B3 virus (CVB3) infection (Yajima et al., 2006). In addition, STAT3 plays a protective role in regulating virus-induced proinflammatory response, as shown in STAT3 knock-out studies (El Kasmi et al., 2006; Kobayashi et al., 2003; Matsukawa et al., 2003). Highly pathogenic avian influenza (HPAI) H5N1 virus induces strong

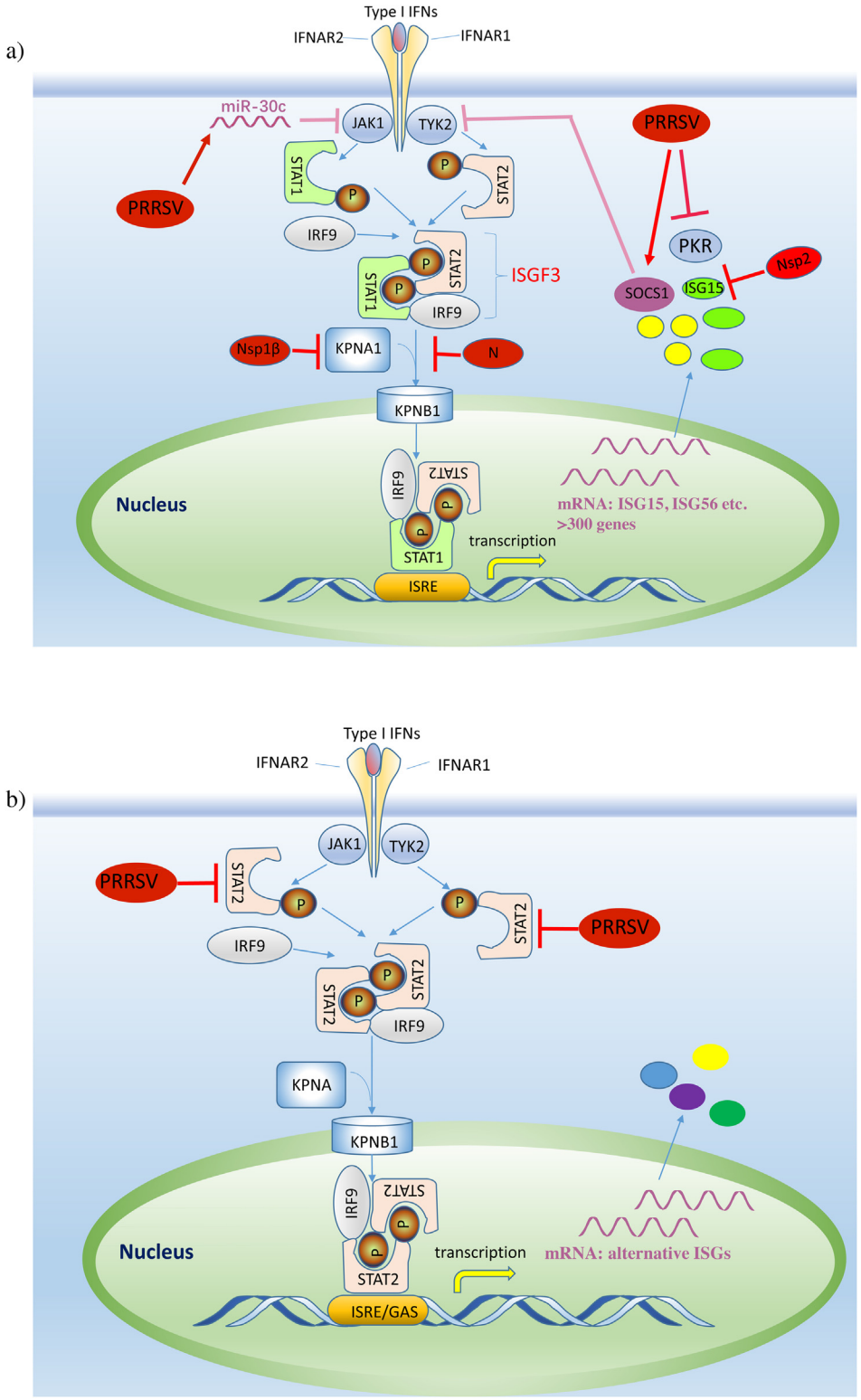

Fig. 1. PRRSV interference with type I IFN-activated JAK-STAT signaling. A. Canonical signaling. IFN-α/β binds to their receptors IFNAR-1 and IFNAR-2 on the cell membrane and activates the JAK-STAT1/STAT2 pathway. The phosphorylated STAT1 and STAT2 form heterodimer, followed by interaction with IRF9 to form interferon-stimulated gene factor 3 (ISGF3). Karyopherin α1 (KPNA1), an adaptor protein binding ISGF3, is essential to mediate the nuclear import of ISGF3 via interaction with karyopherin β1 (KPNB1). The ISGF3 binds to interferon-stimulated response element (ISRE) in DNA to activate transcription of interferon-stimulated genes (ISGs). "P" besides STATs indicates phosphorylation. PRRSV nsp1β inhibits ISGF3 nuclear translocation via inducing degradation of KPNA1. PRRSV N protein also inhibits ISGF3 nuclear translocation. PRRSV nsp2 reduces ISG15 production and conjugation via its deubiquitination activity. PRRSV induces elevation of miRNA miR-30c to downregulate JAK1 and SOCS1 to inhibit JAKs. PRRSV inhibits PKR during its early infection of pulmonary alveolar macrophages. B. STAT1-independent signaling. Type I IFNs activate alternative JAK-STAT2 signaling without STAT1. The ISGF3-like complex binds to ISRE and interferon-gamma-activated sequence (GAS) to activate alternative sets of ISGs. PRRSV reduces STAT2 protein to inhibit this pathway.

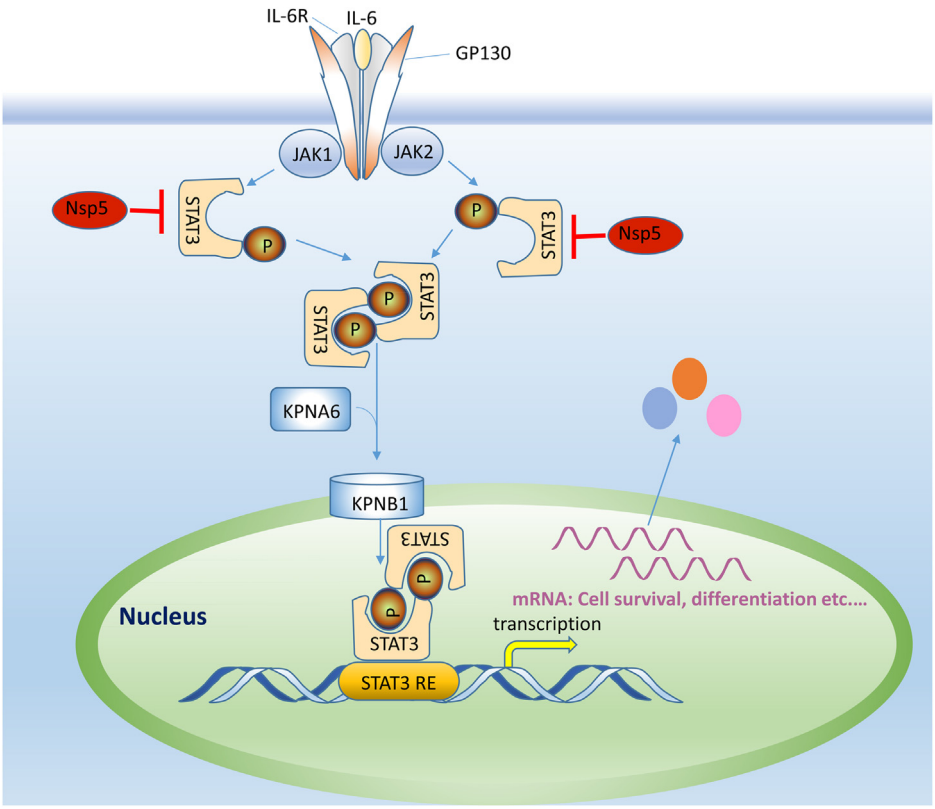

Fig. 2. PRRSV interference with JAK-STAT3 signaling activated by IL-6 family cytokines. IL-6 binds to its receptor IL-6R and gp130, leading to JAK phosphorylation of STAT3, followed by STAT3 homodimer formation. KPNA6 is the adaptor protein to bind to STAT3 and interact with KPNB1 for the nuclear translocation. The STAT3 homodimer binds to STAT3 response element (RE) in DNA to activate transcription of target genes. PRRSV nsp5 induces STAT3 degradation to inhibit JAK-STAT3 signaling.

proinflammatory response in chickens via inhibition of STAT3 phosphorylation (Kuchipudi et al., 2014).

STAT4 is activated by IL-12 and is essential for Th1 cell differentiation (Schindler et al., 2007). Even though its distribution is restrained in myeloid cells, testis and thymus, STAT4 is critical for the host immunity. It is also activated by IL-23 to induce expansion of Th17 cells and the associated autoimmunity (Schindler et al., 2007). Moreover, STAT4 is crucial for the biological effects of macrophage, natural killer cell, mast cell, and dendritic cell as well as IFN-γ production (Liang et al., 2014).

STAT5 is activated by IL-2, IL-3, IL-5 and granulocyte macrophage colony-stimulating factor (GM-CSF), and is essential for regulatory T cell (Treg) differentiation (O'Shea and Plenge, 2012). STAT5 can also be activated by IL-7 and IL-15, contributing to the generation of $CD8^+$ memory cells and B lymphopoiesis (O'Shea and Plenge, 2012; O'Shea et al., 2015). STAT5A and STAT5 B are two highly related proteins and have indispensable roles, especially to the effector and Treg response, for which STAT5 B is dominant (Villarino et al., 2016). Tregs takes charge of maintaining homeostasis and controlling the immune response by restraining immunocompetent effector cells (Belkaid, 2007).

STAT6 is activated by IL-4 and IL-13 and is pivotal for Th2 and Th9 lymphocyte differentiation (O'Shea et al., 2015; Walford and Doherty, 2013) (Fig. 3A). STAT6 has been demonstrated to regulate lung inflammatory responses in animal models (Walford and Doherty, 2013). Moreover, STAT6 contributes to alternative activation of macrophages and lung anti-viral responses in a JAK-independent manner (Chen et al., 2011). Viral or cytoplasmic nucleic acids trigger STING (stimulator of interferon genes) or MAVS (mitochondrial antiviral-signaling protein) to recruit STAT6 to the endoplasmic reticulum, followed by TBK1 (TANK-binding kinase 1) phosphorylation of STAT6 and nuclear translocation (Fig. 3B). Expression of chemokines, including CCL2, CCL20, and CCL26, are then activated to recruit immune cells to combat viral infection (Chen et al., 2011).

1.3. PRRSV

PRRSV is a small, enveloped RNA virus of the genus *Arterivirus*, family *Arteriviridae*, order *Nidovirales* (Faaberg et al., 2012). There are two PRRSV genotypes: Type 1 (European PRRSV) and Type 2 (North American PRRSV), which have around 60% genomic nucleotide identity (Faaberg et al., 2012). In a new proposal to the International Committee on Taxonomy of Viruses (ICTV), PRRSV Type 1 and Type 2 viruses are classified as two separate species: *Porcine reproductive and respiratory syndrome virus 1* and *Porcine reproductive and respiratory syndrome virus 2*, respectively, due to their big genomic difference (Brinton et al., 2015).

PRRSV genome is a linear, non-segmented, single-stranded, and positive-sense RNA in a size of approximately 15 kb (Conzelmann et al., 1993; Faaberg et al., 2012). Over ten open reading frames (ORFs) have been identified in the PRRSV genome. About four-fifths of the genome encode polyproteins that are cleaved into 14 non-structural proteins (nsps) and the 3′-terminal one-fifth encodes eight structural proteins (Lunney et al., 2016).

The main target cells for PRRSV infection *in vivo* are some monocyte/macrophage lineages, mainly pulmonary alveolar macrophages (PAMs) (Lunney et al., 2016; Rossow et al., 1995; Wensvoort et al., 1991). PAMs are important effector immune cells of the innate immune system against pathogens in the lung (Franken et al., 2016). Cytokines like IFN-γ and GM-CSF activate JAK-STAT signaling to regulate macrophage phenotype and

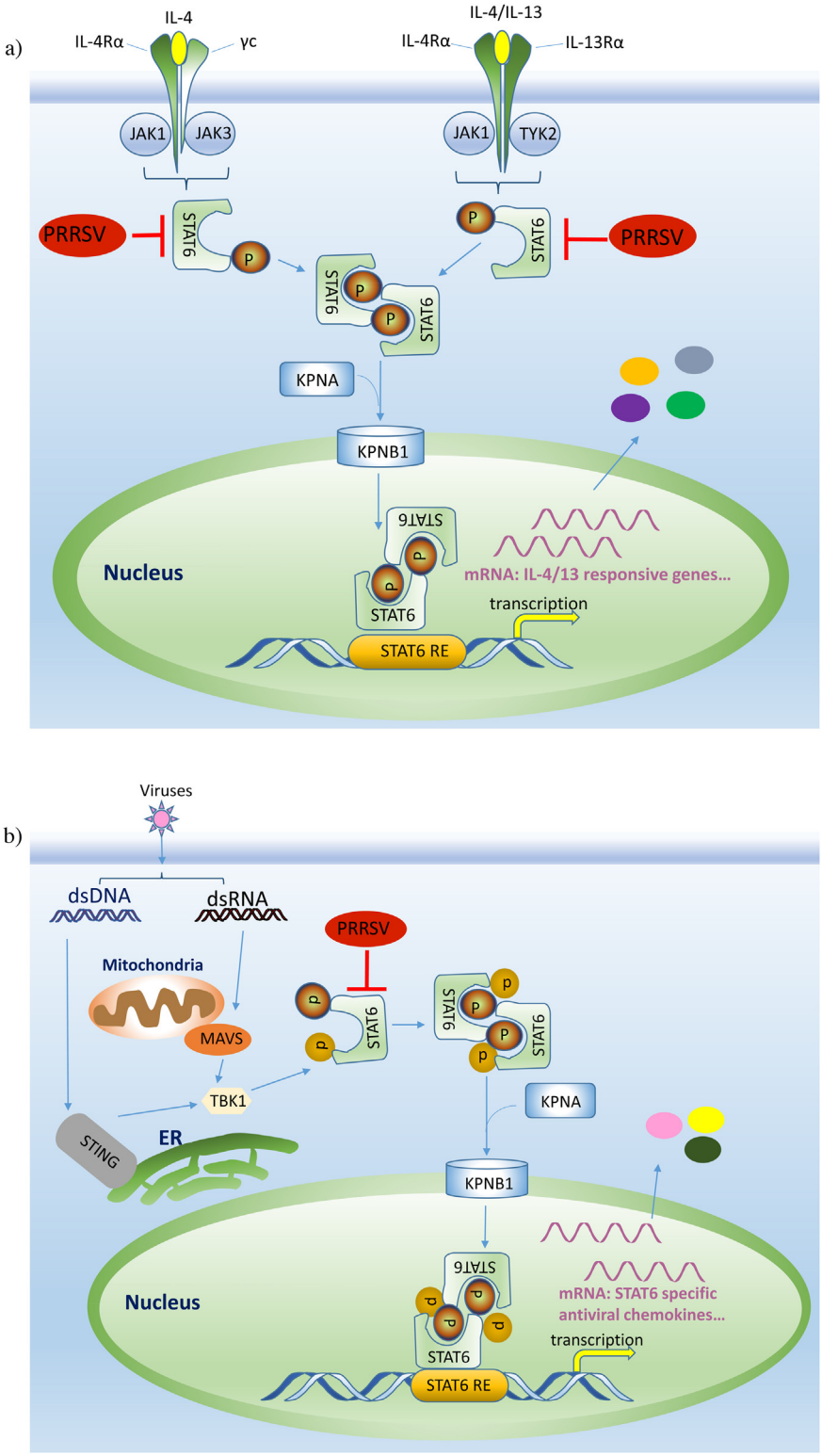

Fig. 3. PRRSV interferes with STAT6 signaling. A. Canonical JAK-STAT6 signaling. IL-4 and IL-13 bind to receptors, leading to JAK phosphorylation of STAT6, followed by homodimer formation and nuclear translocation to activate target genes. PRRSV reduces STAT6 protein level to inhibit the signaling. B. JAK-independent STAT6 signaling. Viral nucleic acids (dsRNA or dsDNA) activate MAVS and STING on mitochondria and endoplasmic reticulum (ER), respectively, leading to TBK1 (TANK-binding kinase 1) phosphorylation of STAT6, followed by homodimer formation and nuclear translocation to activate alternative target genes, including antiviral chemokines. PRRSV reduces STAT6 protein level to inhibit the signaling.

activation (Hu et al., 2007). Activated macrophages secrete immune regulatory cytokines including IL-1β, IL-6, IL-12, TNF-α, and so on (Franken et al., 2016).

2. PRRSV interference with JAK-STAT signaling

To evade the host antiviral response, viruses have evolved numerous strategies including dysregulating JAK-STAT pathway. For example, Epstein-Barr virus (EBV) suppresses IFN signaling by inhibiting the expression of the IFN-γ receptor (Morrison et al., 2001). Paramyxovirus V protein induces STAT protein degradation to evade IFN response (Parisien et al., 2002). Ebola virus VP24 blocks pSTAT1 (phosphorylated STAT1) nuclear translocation by binding KPNA1 (Reid et al., 2006, 2007). The ORF6 product of severe acute respiratory syndrome coronavirus disrupts nuclear import of pSTAT1 by tethering KPNA2 to the endoplasmic reticulum/Golgi membrane (Frieman et al., 2007). Highly pathogenic avian influenza (HPAI) H5N1 virus inducing a strong proinflammatory response in chickens by inhibiting STAT3 phosphorylation (Kuchipudi et al., 2014). PRRSV is known to inhibit IFN-activated JAK-STAT signaling by blocking the ISGF3 nuclear translocation (Patel et al., 2010; Wang et al., 2013b).

2.1. PRRSV inhibits IFN-mediated JAK-STAT signaling

PRRSV inhibits the IFN-activated JAK-STAT signal transduction and ISG expression in both MARC-l45 and PAM cells (Patel et al., 2010; Wang et al., 2013a, 2013b). PRRSV proliferation in MARC-145 cells suppresses JAK-STAT signaling stimulated by IFN-α. The transcripts of ISG15 and ISG56 and protein level of STAT2 in PRRSV-infected cells were much lower than mock-infected cells upon IFN stimulation. PRRSV blocks the nuclear translocation of the IFN-induced ISGF3 complex via nsp1β (Chen et al., 2010; Patel et al., 2010). Avirulent Ingelvac® PRRS MLV has no effect on the IFN-activated JAK-STAT signaling in PAMs (Patel et al., 2010).

Further studies demonstrate that nsp1β inhibits the JAK-STAT signaling via inducing the degradation of KPNA1, which is a critical adaptor protein to mediate the nuclear import of ISGF3 (Wang et al., 2013b) (Fig. 1A). Infection of MARC-145 cells by moderate virulent PRRSV strains VR-2332 and VR-2385 also result in KPNA1 reduction, whereas the Ingelvac® PRRS MLV does not. Nsp1β of VR-2385 induces elevation of KPNA1 ubiquitination and shortening of its half-life. Analysis of nsp1β deletion constructs identifies its N-terminal domain to be involved in the ubiquitin-proteasomal degradation of KPNA1 (Wang et al., 2013b). Sequence analysis of nsp1β from VR-2332 and MLV indicates there are only two different nucleotides, leading to two variable amino acids at residue 19 and 151. Substitution of the N-terminal nucleotide resulting in alteration of residue 19 from valine to isoleucine abolishes the ability of VR-2385 nsp1β to induce KPNA1 degradation and to inhibit IFN-mediated signaling. In contrast, MLV nsp1β has no effect on KPNA1, however, a mutant MLV nsp1β with residue 19 alternation from isoleucine to valine gains the ability to induce KPNA1 degradation (Wang et al., 2013b). These data demonstrate that nsp1β blocks ISGF3 nuclear translocation to inhibit JAK-STAT signaling via inducing KPNA1 degradation and that the residue valine-19 in nsp1β correlates with the inhibition.

Besides nsp1β, other PRRSV proteins including nsp7, nsp12, GP3 and N also inhibit IFN-induced downstream signaling, albeit at a smaller scale (Wang et al., 2013a). The N protein inhibits IFN-activated signaling by blocking STAT1 nuclear translocation (Wang et al., 2013a). Among PRRSV strains, there are variable effects on the IFN-activated JAK-STAT signaling. In MARC-145 cells, PRRSV strains VR-2385, VR-2332, NVSL97-7895, and Lelystad, but not MN184, block the activity of exogenous IFN-α (Wang et al., 2013a). In primary PAMs, strain VR-2385, VR-2332, MN184, and Lelystad, but not NVSL, inhibit the activity of IFN-α. For NVSL97-7895 and MN184, the same virus infection in MARC-145 and PAM cells has variable effects on the IFN-activated signaling. This is not totally unexpected as NVSL strain differs from other PRRSV strains in its failure to induce IL-10 expression *in vivo* (Subramaniam et al., 2011). These two strains might have alternative interacting mechanisms with the JAK-STAT signaling in the two types of cells.

2.2. PRRSV inhibits JAK-STAT3 signaling

Among all the STAT proteins, STAT3 is known as highly pleiotropic in mediating the expression of a variety of genes in response to both cytokines and growth factors, and thus plays a pivotal role in numerous cellular processes including cell survival, proliferation, embryogenesis, and immune responses (Kuchipudi, 2015; Xiong et al., 2014). Thus STAT3 has been found to be the target of some viral pathogens. Measles virus V protein inhibits IL-6 mediated STAT3 signaling (Ulane et al., 2003). V protein of mumps virus prevents responses to IL-6 and v-Src by inducing STAT3 ubiquitination and degradation (Ulane et al., 2005). Rabies virus interferon antagonist P protein inhibits gp130 receptor signaling by interacting with activated STAT3 (Lieu et al., 2013). Inhibition of STAT3 signaling by these viruses and PRRSV can lead to inhibition of a broad spectrum of cytokines and growth factors to thwart host antiviral responses and allow virus replication and spread *in vivo*.

OSM, a member of the IL-6 family activating JAK-STAT3 signaling, enhances the antiviral effects of IFN-α and plays a role in the induction of an adaptive immune response to pathogens (Ikeda et al., 2009; Larrea et al., 2009). Treatment of MARC-145 cells with OSM alone leads to inhibition of PRRSV replication (Yang et al., 2016). To overcome the inhibition, PRRSV uses a strategy to reduce STAT3 protein level.

PRRSV infection of MARC-145 cells and primary PAMs leads to significant reduction of STAT3, whereas it has minimum effect on STAT1 protein level (Yang et al., 2016). Several PRRSV strains tested induce a similar reduction of STAT3 protein level but have no effect on its transcript level. Treatment of the PRRSV-infected cells with MG-132, a proteasomal inhibitor, restores the STAT3 level. The further study identifies that PRRSV nsp5 induces the STAT3 degradation, shown by increased polyubiquitination level and shortened half-life (Yang et al., 2016). As a result, nsp5 inhibited STAT3 signaling. Further study is being undertaken to elucidate the mechanism.

2.3. PRRSV interference with other STATs and JAKs

As aforementioned, other STATs also have important roles in the host immune response. Besides inhibiting JAK-STAT1/STAT2 and JAK-STAT3 signaling, PRRSV might interfere with other STATs. Our preliminary study shows that PRRSV reduces STAT2 and STAT6 protein level (unpublished result). Further study is being undertaken to delineate the mechanisms.

A recent study shows that PRRSV upregulates a host microRNA, miR-30c, which is a negative regulator by targeting JAK1 (Zhang et al., 2016). PRRSV reduces JAK1 expression in infected cells and is expected to affect the phosphorylation of both STAT1 and STAT2. But in our studies, IFN-induced phosphorylation of both STAT1 and STAT2 in PRRSV-infected MARC-145 cells was not affected (Patel et al., 2010). It may play a role *in vivo* as PRRSV infection in pigs leads to elevation of miR-30c in lungs and PAMs and its level corresponds to the viral load (Zhang et al., 2016). This indicates that PRRSV has multiple strategies to block host IFN-signaling.

3. Perspective

PRRSV uses multiple strategies to evade the host innate and adaptive immunity. By interfering with the JAK-STAT signaling, PRRSV may perturb the function of cytokines in the regulation of the host immune response.

3.1. PRRSV and IFN-mediated JAK-STAT signaling

IFNs are essential for antiviral response and targeted by PRRSV at multiple levels ranging from the induction of IFNs, IFN-activated JAK-STAT signaling, to ISGs. PRRSV interference of IFN induction has been reviewed elsewhere (Sun et al., 2012a; Wang and Zhang, 2014). The modulation of innate immunity by nsp1 is conserved in all members of *Arteriviridae* (Han and Yoo, 2014). PRRSV also interferes with ISGs, for example, nsp2 inhibits ISG15 by reducing its production and counteracting its conjugation to cellular proteins (Sun et al., 2012b). PRRSV downregulates interferon-induced double-strand RNA-activated protein kinase (PKR) at its early infection of PAMs (Xiao et al., 2016). PRRSV counteracts interferon-induced transmembrane protein 1 (IFITM1) and Tetherin in MARC-145 cells by nsp3 and E proteins, respectively, (Wang et al., 2014). It is expected that PRRSV may antagonize other ISGs that restrict the virus entry, replication, and spread.

The JAK-STAT signaling is modulated by host suppressive signals, such as suppressors of cytokine signaling (SOCS) proteins, ubiquitin carboxy-terminal hydrolase 18 (USP18), and miRNAs (Croker et al., 2008; Ivashkiv and Donlin, 2014). PRRSV upregulates the suppressive signals to antagonize JAK-STAT pathway. For example, PRRSV infection leads to upregulation of SOCS1 (Wysocki et al., 2012); PRRSV upregulates miRNA miR-30c against JAK1 (Zhang et al., 2016). But overexpression of USP18 leads to a reduction of PRRSV replication (Ait-Ali et al., 2009). Further study needs to be done to determine the mechanism.

The combined effect of multiple perturbations by PRRSV results in efficient PRRSV replication and invasion, and consequently, contributes to the poor induction of protective immune response. Minimizing the interference is expected to improve the host immune response to PRRSV infection. Indeed, PRRSV strain A2MC2, which induces type I IFNs in infected cells *in vitro* and has no inhibitory effect on IFN signaling (Nan et al., 2012), elicits higher virus-neutralizing antibodies than the MLV in pigs (Wang et al., 2013c). Site-directed mutagenesis of R128 and R129 of nsp1β reduced its inhibition of IFN induction and leads to improvement of innate and adaptive immune responses (Li et al., 2016).

3.2. PRRSV antagonizes JAK-STAT3 signaling pathway

As mentioned above, STAT3 has pleiotropic activity and plays important roles in many biological processes. STAT3 is a central regulator of lymphocyte differentiation and function (Kane et al., 2014). STAT3 is needed for activation and maturation of dendritic cells (DCs) and plasmacytoid DCs are considered to be the major source of IFN-α production during viral infection. STAT3 deficiency affects the generation of memory $CD8^+$ T cells (Cui et al., 2011; Siegel et al., 2011) and memory B cells (Avery et al., 2010; Deenick et al., 2013). PRRSV infection induces a weak cell-mediated immune response, in which PRRSV-specific T cells transiently appears two weeks after infection without a change in frequencies of $CD4^+$ and $CD8^+$ T-cells (Xiao et al., 2004). The STAT3 antagonizing may be one of the reasons for PRRSV interference with the development of protective immune response.

PRRSV inhibits STAT3 signaling by inducing degradation of STAT3 but has minimum effect on STAT1 protein level (Yang et al., 2016). This reduction appears to be an intrinsic property of PRRSV as both Type 1 and 2 PRRSV strains are able to downregulate STAT3. PRRSV infection in pigs leads to elevation of IL-10 (Chung and Chae, 2003; Suradhat and Thanawongnuwech, 2003) and induces lung lesions with inflammatory cell infiltration (Halbur et al., 1995). IL-10 signaling via mediator STAT3 results in the generation of regulatory macrophages, which have an anti-inflammatory activity to dampen immunopathology. PRRSV antagonizing STAT3 signaling could interfere with the IL-10 regulatory function and leads to dysregulation of inflammation.

PRRSV nsp5 is responsible for the STAT3 reduction. Nsp5 is a hydrophobic transmembrane protein and can possibly form a membranous structure in the cytoplasm that could be the site for PRRSV replication (Lunney et al., 2016). No direct interaction between nsp5 and STAT3 is identified, which suggests that nsp5 might activate an E3 ligase of STAT3. Further study will reveal the mechanism of the induction of STAT3 degradation.

3.3. PRRSV's effect on STAT2/5/6 signaling

As aforementioned, other than STAT1 and STAT3, other STAT proteins have also been shown to be significant for the host immune response. STAT2 is involved in STAT1-independent signaling by interacting with IRF9 to drive the expression of ISRE-containing genes (Bluyssen, 2015; Fink and Grandvaux, 2013). As PRRSV reduces STAT2 protein, we expect it inhibits the STAT1-independent antiviral signaling.

PRRSV's effect on the signaling of STAT4, STAT5 and STAT6 has not been determined yet. The main target cells for PRRSV infection are certain lineages of monocytes/macrophages *in vivo*. The PRRSV effect on JAK-STAT signaling in T cells would be indirect, such as by exosomes from infected cells (Garcia-Nicolas et al., 2016; Montaner-Tarbes et al., 2016). But its interference of the JAK-STAT signaling in infected macrophages would have significant consequence as the response of PAMs against viral or bacterial pathogens is critical in determining the outcome of infection in the host. Cytokines like IFN-γ and GM-CSF activate JAK-STAT signaling to regulate macrophage phenotype and activation (Hu et al., 2007). Activated macrophages secrete immune regulatory cytokines including IL-1β, IL-6, IL-12, TNF-α and so on (Franken et al., 2016).

STAT6 has been demonstrated to have JAK-independent antiviral signaling (Chen et al., 2011). PRRSV is expected to inhibit this alternative STAT6 signaling, which may contribute to the PRRSV evasion. Indeed, PRRSV reduces STAT6 protein level in infected MARC-145 cells (unpublished result). Further study will examine the mechanisms of the interference of STAT6 signaling.

4. Conclusion

In conclusion, PRRSV perturbs JAK-STAT signaling pathways by disturbing STATs protein level and their nuclear translocation. PRRSV inhibits IFN-activated JAK-STAT signaling by blocking nuclear translocation of ISGF3 (Patel et al., 2010; Wang et al., 2013b). Recently, we discovered that PRRSV inhibits JAK-STAT3 signaling via inducing degradation of the STAT3 protein (Yang et al., 2016). We also noticed that STAT2 and STAT6 protein levels were much lower in PRRSV-infected cells than uninfected controls (unpublished results). PRRSV interaction with the JAK-STAT signaling pathways is complex and consequences would be possibly depending on the context of the milieu during infection.

Despite substantial efforts to study and control PRRS, no production or vaccination regimen has demonstrated sustaining success (Renukaradhya et al., 2015a, 2015b). This is likely in part due to the PRRSV poor induction of protective immune response, allowing for PRRSV replication, spread, and persistence in infected populations. Elucidation of the mechanisms of PRRSV evasion of JAK-STAT signaling would yield insightful information, which may

facilitate the development of improved vaccines or therapeutics against PRRSV and other pathogens.

Conflicts of interest

None.

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