Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Virus Research 202 (2015) 101–111

Contents lists available at ScienceDirect

Virus Research

journal homepage: www.elsevier.com/locate/virusres

Regulation and evasion of antiviral immune responses by porcine reproductive and respiratory syndrome virus

Chen Huang[a,b], Qiong Zhang[a,b], Wen-hai Feng[a,b,*]

[a] State Key Laboratory of Agrobiotechnology, College of Biological Sciences, China Agricultural University, Beijing 100193, China
[b] Department of Microbiology and Immunology, College of Biological Sciences, China Agricultural University, Beijing 100193, China

ARTICLE INFO

Article history:
Available online 18 December 2014

Keywords:
PRRSV
Immune evasion
Type I IFNs
Apoptosis
Innate immunity
Adaptive immunity

ABSTRACT

Virus infection of mammalian cells triggers host innate immune responses to restrict viral replication and induces adaptive immunity for viral elimination. In order to survive and propagate, viruses have evolved sophisticated mechanisms to subvert host defense system by encoding proteins that target key components of the immune signaling pathways. Porcine reproductive and respiratory syndrome virus (PRRSV), a RNA virus, impairs several processes of host immune responses including interfering with interferon production and signaling, modulating cytokine expression, manipulating apoptotic responses and regulating adaptive immunity. In this review, we highlight the molecular mechanisms of how PRRSV interferes with the different steps of initial antiviral host responses to establish persistent infection in pigs. Dissection of the PRRSV–host interaction is the key in understanding PRRSV pathogenesis and will provide a basis for the rational design of vaccines.

1. Introduction

Since described in USA in 1987, porcine reproductive and respiratory syndrome (PRRS) has now been one of the most important diseases in pigs, leading to significant economic losses in swine industry worldwide (Albina, 1997; Pejsak et al., 1997; Rossow, 1998). In 2005, the annual costs of PRRS for the American swine industry were approximately 560 million dollars (Neumann et al., 2005), and recently, the estimated costs are increased to about $664 million per year in the United States (Jiang et al., 2013). In the past twenty-seven years, PRRS has emerged in almost all of the pig-producing countries (Bilodeau et al., 1991; Cho and Dee, 2006; Kuwahara et al., 1994). In 2006, a highly pathogenic PRRSV (HP-PRRSV) strain with discontinuous 30 amino acid depletion in nsp2 protein associated with porcine high fever syndrome (PHFS) was reported in China, and overwhelmed swine industries in China and Vietnam (Huang and Meng, 2010; Li et al., 2007b; Tian et al., 2007). The clinical symptoms of typical PRRS are reproductive failure in sows and severe respiratory disease and poor growth performance in piglets (Done and Paton, 1995; Pejsak et al., 1997). For the high fever syndrome, it is characterized by high fever, high morbidity, and high mortality (Tian et al., 2007).

The causative agent, porcine reproductive and respiratory syndrome virus (PRRSV), was identified in 1991 in the Netherlands (Wensvoort et al., 1991) and 1992 in the United States (Morrison et al., 1992). According to the sequence analysis, PRRSV is grouped into two genotypes, the type 1 European PRRSV (the prototype is Lelystad virus (LV)) and the type 2 North American PRRSV (the prototype is VR2332). PRRSV is an enveloped positive single-stranded RNA virus and belongs to the genus *Arterivirus*, family *Arteriviridae*, order *Nidovirales*. The genus *Arterivirus* also includes equine arteritis virus (EAV), lactate dehydrogenase-elevating virus (LDV), and simian hemorrhagic fever virus (SHFV) (Cavanagh, 1997; Plagemann and Moennig, 1992; Snijder and Meulenberg, 1998). PRRSV genome is approximately 15.4 kb in length and has at least 10 open reading frames (ORFs) (Yun and Lee, 2013). ORF1a and ORF1b, which constitute about 75% of the genome, encode two polyprotein precursors: pp1a and pp1ab. pp1a and pp1ab are considered to be cleaved into at least 16 nonstructural proteins (nsp1α, nsp1β, nsp2-6, nsp2TF, nsp2N, nsp7a, nsp7b and nsp8-12) upon infection by viral proteases nsp1α, nsp1β, nsp2, and nsp4. ORF2a, ORF2b, ORF3-7, and ORF5a encode eight structural proteins: a small, non-glycosylated E protein, five glycosylated membrane proteins (GP2-GP5 and GP5a), a non-glycosylated membrane protein (M), and the nucleocapsid protein (N) (Dokland, 2010; Fang and Snijder, 2010; Fang et al., 2012b; Li et al., 2014; Wei et al., 2013). These PRRSV proteins are involved in virus entry, replication and

* Corresponding author at: State Key Laboratory of Agrobiotechnology, College of Biological Science, China Agricultural University, Beijing 100193, China.
Tel.: +86 10 62733335; fax: +86 10 62732012.
E-mail address: whfeng@cau.edu.cn (W.-h. Feng).

http://dx.doi.org/10.1016/j.virusres.2014.12.014
0168-1702/

viral particle assembly processes. In addition, some of the proteins are multi-functional and shown to play modulatory roles in host immune responses.

In this review, we will focus on the interaction between host immune system and PRRSV, and describe the molecular mechanisms used by PRRSV and its proteins to modulate host immune responses and signaling pathways, and discuss the implications that these modulations have on viral pathogenesis and the rational design of protective vaccines.

2. Host immune responses against virus infection

Virus infection results in the activation of pattern recognition receptors (PRRs) by recognizing specific pathogen-associated molecular patterns (PAMPs) to initiate antiviral signaling cascades, triggering the production of cytokines including interferons (IFNs) and chemokines (Kawai and Akira, 2006; Pichlmair and Reis e Sousa, 2007; Tenoever and Maniatis, 2006; Yan and Chen, 2012). The induction of critical cytokines is essential for antiviral innate immunity to control virus infection in the early phase and facilitate the adaptive immune system (Hoebe et al., 2004; Kabelitz and Medzhitov, 2007).

Type I interferons are important antiviral cytokines that represent one of the first lines of defense to limit viral replication and spread, thus contributing to the protection of host from infections. The induction of type I IFNs depends on sensors detecting viral nucleic acid, which is generated as genome or intermediates of viral transcription or replication (Akira et al., 2006). Two intracellular PRRs, the retinoic acid inducible gene-I (RIG-I) and melanoma differentiation associated gene 5 (MDA5), act as sentinels for detecting viral RNA in the cytoplasm (Loo and Gale, 2011; Takeuchi and Akira, 2008). Activated RIG-I and MDA5 recruit virus-induced signaling adaptor (VISA, also known as MAVS, Cardif, and IPS-1) via CARD-CARD (caspase recruitment domain) interaction (Kawai et al., 2005; Seth et al., 2005; Xu et al., 2005). VISA is localized in mitochondria and acts as a bridge to link RIG-I-like RNA helicase (RLH) and the TNF receptor associated factor 3 (TRAF3) complex, which subsequently activates transcriptional factors IRF3 and IRF7 in a TRAF family-member-associated NF-kB activator (TANK) binding kinase 1 (TBK1)- and IKKi-dependent manner (Akira et al., 2006). VISA also interacts with TRAF2/6 complex, which is required for the activation of NF-κB (Edwards et al., 2007). Alternative endosome–lysosome PRRs, TLR3 and TLR7 recognize double-stranded RNA and single-stranded RNA, respectively, leading to the dimerization of receptors and recruitment of adaptor TRIF or MyD88 (Diebold et al., 2004; Kawai and Akira, 2010; Oshiumi et al., 2003). The stimulation triggers the assembly of signaling complexes and initiation of signaling cascades, resulting in the activation and nuclear translocation of IRF3/IRF7, NF-κB, and AP-1 to induce the transcription of type I IFNs (Honda et al., 2006). The crucial effort of type I IFNs on antiviral responses results from the activation of JAK/STAT signaling, leading to the expression of interferon-stimulated genes (ISGs) (Stark and Darnell, 2012; Takaoka and Yanai, 2006). These ISGs are involved in the amplification and regulation of the IFN responses, and interfere with several steps of the viral life cycle (Sadler and Williams, 2008; Schoggins and Rice, 2011; Schoggins et al., 2011).

The activation of PRRs also triggers the inflammatory cytokine and chemokine productions (Takeuchi and Akira, 2010). Recognition of viral molecules by TLRs recruits specific adaptor to the receptors, resulting in the production of proinflammatory cytokines via the TRAF6-TAK1-NF-κB pathway (Deng et al., 2000; Wang et al., 2001). Simultaneously, TGF-β-activated kinase 1 (TAK1) activates the MAPK (JNK, p38, and ERK) pathway, leading to the activation of AP-1. The adaptor of RIG-I like receptors (RLRs), VISA, also interacts with the Fas-associated death domain protein (FADD) to induce NF-κB activation and modulate the transcription of proinflammatory cytokines such as IL-1β, IL-6 and TNFα (Takahashi et al., 2006). Different from IL-6 and TNFα, the production of secreted IL-1β requires the cleavage of pro-IL-1β by a protease, caspase-1, which is activated independent of TLR and RLR signaling. Inflammasome, which is composed of nucleotide oligomerization domain (NOD)-like receptors, apoptosis-associated speck-like protein containing a CARD (ASC) adaptor and caspase-1, induces caspase-1 activation to mediate the maturation of pro-IL-1β (Rathinam et al., 2012). The secretion of proinflammatory cytokines is responsible for amplifying the innate immune responses to virus infection and shaping the adaptive immune responses to follow.

3. Modulation of immune responses by PRRSV

Epidemiologic studies have revealed that conventional strains of PRRSV often develop a persistent infection after an acute infection lasting for 3–4 weeks (Cho and Dee, 2006; Rossow, 1998; Wills et al., 1997). During persistent infection, viremia is absent and virus replication is restricted in some immune privileged lymphoid tissues (Beyer et al., 2000; Rowland et al., 2003). The persistence of the virus within pigs and herds is often associated with the recurrence of secondary viral and bacterial infections (Albina et al., 1994; Stevenson et al., 1993). This reflects the fact that PRRSV has evolved mechanisms to evade and suppress host immune responses.

3.1. Escape from innate immunity

3.1.1. Suppression of type I IFN induction and signaling

Interferons have various functions in activating innate immune responses against viral infection (Theofilopoulos et al., 2005). In particular, type I IFNs block viral replication and spread by inducing multiple antiviral proteins that interfere with every step of the viral infection. Previous studies have shown that PRRSV is sensitive to interferons, and recombinant porcine IFNβ or synthetic double stranded RNAs can inhibit PRRSV replication and protect pigs from PRRSV infection (Albina et al., 1998; Miller et al., 2004; Overend et al., 2007). In order to propagate and spread in hosts, PRRSV has evolved several strategies to antagonize type I IFN responses (see Table 1). These strategies include delaying the PRR detection, interfering with detection and signaling pathways of IFN induction, inhibiting IFN-mediated signaling pathways, and blocking the action of IFN-induced genes with antiviral activity.

3.1.1.1. Delaying the PRR detection. Invading agents are detected by cell membrane or intracellular PRRs. RNA sensors including

Table 1
Antagonism of type I IFN responses by PRRSV.

Viral proteins	Function
nsp1	Inhibits IRF3 phosphorylation and nuclear translocation Mediates CBP degradation Inhibits NF-κB-responsive promoter activation Induces degradation of karyopherin-α1 and inhibits nuclear translocation of ISGF3
nsp2	Prevents the polyubiquitination and degradation of IκBα Suppresses activation of IRF-3 Interferes with ISG15 conjugation to cellular proteins
nsp4	Mediates the cleavage of NEMO and suppresses NF-κB activation
nsp11	Inhibits NF-κB and IRF3 promoter activation
N	Inhibits poly(I:C)-mediated IRF3 phosphorylation and nuclear translocation

endosome–lysosome TLR3 and TLR7, cytosol RIG-I and MDA5, may play vital roles in recognizing and responding to PRRSV infection. Many viruses such as swine transmissible gastroenteritis virus (TGEV) and Sendai virus (SeV) induce activation of PRR signaling within hours of virus infection (Albina et al., 1998). However, virulent PRRSV strains, especially highly pathogenic strain JXwn06, appear to delay the activation of PRR, which is of benefit to the viral replication within cells during the early stages of infection (Huang et al., 2014). Previous publications have shown that SARS-CoV (also belonging to the order Nidovirales) infection leads to the formation of double membrane vesicles (DMVs) and proteins involved in virus replication (nsp3, nsp5, and nsp8) are located mainly outside of DMVs (Knoops et al., 2008; Perlman and Netland, 2009). These vesicles contribute to viral replication and help hide the viral RNA from cellular recognition and delay the antiviral IFN production. Similarly, in arterivirus life cycle, open reading frame 1a (ORF1a)-encoded subunits of the arterivirus replicase induce endoplasmic reticulum-derived DMVs, which scaffold the viral replication complex (Kroese et al., 2008; Pedersen et al., 1999). These reports suggest that hiding the viral RNA from PRR recognition of nidoviruses delays IFN induction. However, the precise mechanisms by which PRRSV evades PRRs detection need to be determined.

3.1.1.2. Inhibition of IFN production. The production of type I IFNs depends on activation of the transcription factors IRF-3/7, NF-κB and AP-1 through either TLRs or RLRs pathways. In PRRSV-infected macrophages and PBMCs, IFNα is undetectable when cells are superinfected with TGEV, a known inducer of Type I IFNs (Albina et al., 1998). Moreover, PRRSV has been reported to repress the ability of porcine pDC to mount type I IFN responses to itself as well as to TGEV, and a TLR9 agonist, ODN D19 (Calzada-Nova et al., 2011). Five PRRSV proteins have been identified and characterized as IFN antagonists, including one structural protein (N) and four non-structural proteins (nsp1, nsp2, nsp4 and nsp11).

Nsp1 has been considered as the strongest antagonist to inhibit IFNβ production. PRRSV nsp1 can be auto-cleaved into two proteins nsp1α and nsp1β, each of which includes a papain-like cysteine protease domain, called PCPα and PCPβ, respectively (den Boon et al., 1995; Ziebuhr et al., 2000). Nsp1α and nsp1β have been shown to be involved in suppressing IFNβ luciferase activity (Chen et al., 2010). IRF3 (Ser 396) phosphorylation and nuclear translocation are inhibited by nsp1β (Beura et al., 2010). Nsp1 expression also inhibits the activation of NF-κB-responsive promoter (Song et al., 2010). Furthermore, nsp1 mainly localizes into the cell nucleus after 10 h post-infection (Chen et al., 2010), indicating that the nuclear form may interact with the host factors in the nucleus. Kim et al. have reported that nsp1 inhibits IRF3 association with CREB-binding protein (CBP) in the nucleus and mediates CBP degradation to block the recruitment of CBP for enhanceosome assembly, leading to the inhibition of IFN transcriptional activation. However, CBP degradation is not due to nsp1 PCP activity but rather mediated via the proteasome-dependent degradation pathway (Kim et al., 2010).

Nsp2 is the largest and the most variable non-structural protein in PRRSV, with only ~32% identity between subtypes (Allende et al., 1999). The highly pathogenic PRRSV reported in 2006 outbreaks in China contains two non-contiguous deletions (30 amino acids) in the nsp2 hypervariable region (Li et al., 2007b; Tian et al., 2007), and these deletions serve as genetic markers for differentiation from other conventional PRRSV. Nsp2 is a papain-like protease belonging to the ovarian-tumor domain deubiquitinase superfamily (Frias-Staheli et al., 2007; Makarova et al., 2000). Previous study has shown that nsp2 antagonizes IFNβ induction by interfering with the NF-κB signaling pathway in HEK-293T cells (Sun et al., 2010). The precise mechanism is that the nsp2 OTU domain, which possesses ubiquitin-deconjugating activity, has the ability to inhibit NF-κB activation by interfering with the polyubiquitination process of IκBα, leading to the prevention of IκBα degradation. Nsp2 also inhibits IFNβ production by suppressing the activation of the IRF-3 pathway induced by SeV and the cysteine protease domain (PL2) is required for this function (Li et al., 2010). On the contrary, Fang et al. have found that nsp2 of HP-PRRSV strain WUH3 activates NF-κB in MARC-145 and HeLa cells through inducing IκBα degradation and p65 translocation to the nucleus, leading to the expression of IL-6, IL-10 and COX-2. Further studies have demonstrated that 30-aa deletion of HP-PRRSV is not associated with NF-κB induction, but the hypervariable region (HV) is essential for NF-κB activation (Fang et al., 2012a). Our results have also revealed that nsp2 of HP-PRRSV strain JXwn06 has no inhibitory effect on IFNβ production induced by poly(I:C) in HeLa cells (Huang et al., 2014). The possible explanation for these seemingly opposite results is that nsp2 sequence varies among different strains. However, the effect of nsp2 on host innate immunity needs to be further investigated.

PRRSV nsp4, which belongs to the member of the chymotrypsin-like serine proteases (3CLSP), is a multifunctional protein that participates in polypeptide protein process and viral replication (Fang and Snijder, 2010; Snijder et al., 1996). Nsp4 contains a canonical catalytic triad that is composed of Ser118, His39, and Asp64, and cleaves specific substrate of the 3C-like cysteine proteases, a subgroup of chymotrypsin-like enzymes named after the picornavirus 3C proteases (Tian et al., 2009). Previous studies have revealed that the 3C protease participates in a number of biological processes. For example, it can inhibit host cell polyadenylation by mediating the cleavage of CstF-64, a critical factor for 3′ pre-mRNA processing in a cell nucleus (Weng et al., 2009), trigger apoptosis through caspase activation, and suppress type I IFN expression by cleaving key factors of the signaling pathways (Belsham et al., 2000; Lei et al., 2013; Li et al., 2002; Mukherjee et al., 2011). Beura et al. have shown that PRRSV nsp4 inhibits IFNβ promoter activity activated by IRF3 overexpression in HeLa cells (Beura et al., 2010). Recently, we have found that nsp4 antagonizes IFNβ and NF-κB activation in HeLa and porcine CRL-2843 cells by inhibiting IκBα phosphorylation and p65 translocation to the nucleus. The inhibition depends on 3C-like serine protease catalytic activity of nsp4, and site or deletion mutants abolish its inhibitory property. We further show that nsp4 mediates the cleavage of NF-κB essential modulator (NEMO), a regulatory subunit of IKKs complex, leading to the suppression of NF-κB activation and IFNβ production (Huang et al., 2014). Chen et al. have also found that nsp4 suppresses IFNβ transcription by blocking NF-κB activation, and the amino acid at residue 155 in nsp4 is essential for the effect (Chen et al., 2014). In addition, they show that nsp4 from different pathogenic PRRSV strains has differential ability to inhibit IFNβ expression. In agreement with this observation, our results show that nsp4 of HP-PRRSV JXwn06 has greater inhibitory effect on IFNβ induction than nsp4 from the less pathogenic PRRSV CH-1a. These data imply that the inhibitory property on IFNβ induction by PRRSV nsp4 may be correlated with PRRSV pathogenicity.

Nsp11 contains the nidovirus uridylate-specific endoribonuclease (NendoU) activity, a genetic marker unique to Nidoviruses (Nedialkova et al., 2009). Nsp11 has been examined for its inhibition role in IFNβ production. In MARC-145 cells, nsp11 overexpression inhibits poly(I:C) or IKKε-induced activations of IFNβ promoter and IRF3 dependent promoter, and NendoU activity in nsp11 is essential for the suppression (Shi et al., 2011). Beura et al. have found that nsp11 is able to inhibit NF-κB promoter activation (Beura et al., 2010). These results have also been confirmed by another report (Sun et al., 2014). All of these are in support of the opinion that nsp11 functions in IFN down-regulation. However, the precise mechanisms for nsp11 to interact with host immune responses remain to be further elucidated.

The nucleocapsid (N) protein is a small basic protein with 123 amino acids, and possesses a N-terminal RNA-binding domain and a C-terminal dimerization domain (Yoo et al., 2003). N is the structural component of the viral capsid and participates in nucleocapsid assembly and virus infectivity. Similar to nsp1, N protein is localized in the cytoplasm and the nucleus (Rowland et al., 1999), suggesting that the nuclear translocation of N may have effects on the modulation of host antiviral responses. Supporting this note, the ability of N to circumvent the innate immunity by suppressing type I IFN induction has been verified. N protein suppresses IFNβ expression by inhibiting poly(I:C)-mediated IRF3 phosphorylation and nuclear translocation in immortalized porcine alveolar macrophages (Sagong and Lee, 2011). However, whether the nuclear localization of N protein is critical for its ability to modulate the IFN responses by inhibiting IRF3 activation needs to be investigated.

3.1.1.3. Inhibition of IFN responses. The binding of type I IFNs to the IFNAR on the surface of cells that secret type I IFNs or nearby cells triggers the activation of the JAK/STAT signal pathway, resulting in the expression of a wide variety of interferon-stimulated genes (ISGs) that can establish antiviral and immune-regulatory states in host cells. However, PRRSV is shown to efficiently inhibit the downstream signal transduction of type I IFNs. IFNα-induced ISG15 and ISG56 production is suppressed in PRRSV-infected MARC-145 cells and PAMs. IFNα stimulation increases the expression of STAT2, whereas STAT2 protein in PRRSV-infected cells after IFNα treatment remains at the control level (Patel et al., 2010). PRRSV and its viral protein nsp1β have the ability to block nuclear translocation of ISGF3 heterotrimers. The mechanism is that the N-terminal domain of nsp1β induces degradation of karyopherin-α1 (KPNA1, also known as importin-α5), which mediates nuclear import of ISGF3 (Wang et al., 2013b). Nsp1β of different PRRSV strains has variable effect on JAK/STAT signaling pathway. Two PRRSV strains VR-2332 and VR-2385 infections result in KPNA1 reduction, whereas an avirulent strain Ingelvac PRRS MLV does not. However, MLV reduces the level of ISG15 and ISG56 transcripts induced by IFNs in MARC-145 cells, implying that other mechanisms might be responsible for the suppression of IFN signaling. Many viruses are able to inhibit type I IFN signaling by inducing negative regulators of JAK/STAT signaling (Bode et al., 2003; Pauli et al., 2008; Yokota et al., 2004). However, little is known about the effects of PRRSV infection on up-regulation of these negative regulators.

3.1.1.4. Impairing functions of antiviral ISG. PRRSV can target individual downstream ISGs to interfere with host antiviral responses. ISG15, an ubiquitin-like protein, is one of the highly expressed proteins that function as an effector molecule in host cell responses to viral infection (D'Cunha et al., 1996; DCunha et al., 1996; Zhao et al., 2013). ISG15 conjugation (ISGylation) to substrate proteins follows a process similar to that of ubiquitin conjugation by utilizing an ubiquitin-activating enzyme (UbE1L, E1) (Pitha-Rowe et al., 2004), an ubiquitin-conjugating enzyme (UbCH8, E2) (Zhao et al., 2004), and an ubiquitin ligase (HERC5, E3) (Wong et al., 2006). ISG15 and/or ISGylation of cellular proteins play important roles in establishing an antiviral state in infected cells. In MARC-145 cells, overexpression of ISG15 interferes with PRRSV replication. PRRSV infection induces ISG15 expression in a relative short time but returns to a near-baseline level after 24 h post infection and seems to inhibit ISG15 conjugation, suggesting that PRRSV counters the antiviral effect of ISG15 and ISGylation. PRRSV nsp2 protein, which has a PLP2-DUB domain possesses deISGylation activity, is responsible for interfering with ISG15 conjugation to cellular proteins (Sun et al., 2012).

3.1.2. Modulation of other cytokines production

3.1.2.1. Up-regulation of IL-10. Interleukin-10 (IL-10), also known as human cytokine synthesis inhibitory factor (CSIF), is a crucial immuno-regulatory cytokine and can be produced by several cell types, including monocytes/macrophages, dendritic cells (DCs), and T and B cells (Conti et al., 2003; Ouyang et al., 2011; Saraiva and O'Garra, 2010). IL-10 can inhibit the production of numerous inflammatory cytokines and counter adaptive immunity, such as antigen presentation and cell-mediated immune responses (Moore et al., 2001; Sabat et al., 2010). Accumulating evidence has revealed that PRRSV significantly induces IL-10 expression in vivo and vitro (Flores-Mendoza et al., 2008; Suradhat and Thanawongnuwech, 2003; Suradhat et al., 2003; Thanawongnuwech and Thacker, 2003; Wang et al., 2011). Zhou et al. have found that inoculation with recombinant adenoviruses (rAds) expressing nsp1 (rAd-nsp1) increases IL-10 secretion and decreases IFNγ secretion in pigs, implicating that nsp1 induces IL-10 expression in vivo (Zhou et al., 2012). Previous studies have also shown that IL-10 gene expression is up-regulated in MoDCs and PAMs transfected with the plasmid encoding N protein. Furthermore, recombinant N protein induces IL-10 expression and increases the number of IL-10-producing cells in cultured PBMCs and MoDCs (Wongyanin et al., 2012). Our laboratory shows that PRRSV CH-1a strain activates IL-10 production in PAMs, BMDMs, and MDMs at both mRNA and protein levels. We find that PRRSV-stimulated IL-10 production is dependent on p38 MAPK and NF-κB signaling pathways. By screening PRRSV nonstructural and structural proteins, GP5 is identified as an IL-10 inducer. Overexpression of GP5 induces the phosphorylation of p38 (Hou et al., 2012b). These results are also confirmed by another lab at the same time (Song et al., 2013). The authors find that HP-PRRSV strain WUH3 induces IL-10 production at both mRNA and protein levels in PAMs, and the TLR-MyD88-NF-κB signaling cascade may be required for PRRSV-induced IL-10 expression (Song et al., 2013).

3.1.2.2. Down-regulation of TNFα. Tumor necrosis factor α (TNFα) is a proinflammatory cytokine secreted by a wide variety of cells including macrophages and activated T cells. The pleiotropic function of TNFα is attributed to the promotion of an antiviral state in uninfected neighboring cells, recruitment of lymphocytes to the foci of infection, selective cytolysis of virus-infected cells, and modulation of apoptosis/survival of cells (Natoli et al., 1998; Smith et al., 1994; Toews, 2001). Previous study has revealed that addition of recombinant porcine TNFα to cultures clearly reduces PRRSV replication (Lopez-Fuertes et al., 2000). Therefore, it is unsurprising that PRRSV has evolved anti-TNF strategies.

Increasing evidence has demonstrated the inhibitory effect of PRRSV on TNFα production. In acute phase of PRRSV-infected pigs, TNFα is poorly expressed (Gomez-Laguna et al., 2010). The induction of TNFα by LPS and PMA is significantly suppressed by PRRSV in porcine macrophages (Hou et al., 2012a; Lopez-Fuertes et al., 2000). PRRSV selectively inhibits TNFα expression activated by porcine pDC exposed to TGEV or a TLR9 agonist (Calzada-Nova et al., 2011). It has also been demonstrated that the viral protein nsp1 is involved in the down-regulation of TNFα production. In this work, the authors find that both constitutive subunits (nsp1α and nsp1β) of nsp1 inhibit the activation of TNFα promoter by modulating the activities of transcription factors NF-κB and Sp1, respectively (Subramaniam et al., 2010). Our study also reveals that HP-PRRSV impairs TLR4- and TLR3-stimulated TNFα release through altered ERK regulation. Furthermore, HP-PRRSV strains, HV and JXwn06, are weaker inducers of TNFα production compared to the conventional strain CH-1a, which may partially contribute to the pathogenesis of HP-PRRSV (Hou et al., 2012a).

3.1.3. Modulation of apoptosis

Apoptosis, a process of programmed cell death in multicellular organisms, is a strictly regulated mechanism of cell death that involves a complex network of biochemical pathways (Hotchkiss and Nicholson, 2006; Tait and Green, 2010). The main role of apoptosis is the development and maintenance of homeostasis. Moreover, apoptosis also plays an important role in the pathogenesis of several viral infections (Rudin and Thompson, 1997), and is considered to be a crucial innate defense mechanism that inhibits viral replication and eliminates virus-infected cells (Thomson, 2001). Therefore, many viruses have evolved strategies to prevent or delay apoptosis during replication, ensuring cell survival until sufficient progeny virus is produced (Banadyga et al., 2009; Cai et al., 2011; Shen et al., 2013). PRRSV confers protection to PRRSV-infected PAMs against staurosporine-induced apoptosis, indicating that PRRSV stimulates anti-apoptotic pathways in macrophages at the early stage of infection. PRRSV replication might partially contribute to the inhibition of apoptosis in PRRSV-infected cells, because UV-inactivated virus induces low levels of anti-apoptosis (Costers et al., 2008). Another study shows that activation of JNK signaling pathway is important in apoptosis induction of the host cells in responses to PRRSV infection (Yin et al., 2012). However, at the early stage of PRRSV infection, p53 and Akt are activated as negative regulator of ER-dependent JNK activation, which is in favor of the virus replication (Huo et al., 2013). In cell line MARC-2a stably expressing GP2a, the percentage of apoptotic cells is significantly decreased, suggesting that GP2a protein likely plays a role in apoptotic inhibition exerted by PRRSV (Pujhari et al., 2014).

On the contrary, some viruses induce apoptosis to enhance virus transmission and avoid immune responses (Jan et al., 2000; Medigeshi et al., 2007; Metz et al., 2014). Apoptosis induction in host cells is an important cellular event in the pathogenesis of PRRSV (Suarez, 2000). Apoptosis has been observed in the lungs and thymus of PRRSV-infected pigs (Labarque et al., 2003; Wang et al., 2014). PRRSV also triggers apoptosis in PAMs and MARC-145 cells at the late stage of infection (Costers et al., 2008). A key event in the induction of apoptosis signals is the activation of a family of pro-apoptotic proteases termed caspases (Budihardjo et al., 1999). The data generated by our laboratory show that PRRSV nsp4 is a critical apoptosis inducer and has effect on the activation of caspase-3, -8, and -9 (Ma et al., 2013), which is in agreement with the previous publication that PRRSV infection activates caspase cascades (Costers et al., 2008). The ability of nsp4 to induce apoptosis is significantly impaired by His39, Asp64, and Ser118 mutations in nsp4, revealing that 3C-like protease activity is essential for nsp4 to trigger apoptosis. We also find that apoptosis occurs in both infected and non-infected cells, suggesting that apoptogenic cytokines, such as TNFα, may be induced and involved in this process. Yin et al. have shown that PRRSV infection activates JNK pathway in MARC-145 cells, and PRRSV-induced JNK activation is associated with ROS generation (Huo et al., 2013). Further studies have demonstrated that Bcl-2 family anti-apoptotic proteins Bcl-xl and Mcl-1 are down-regulated by PRRSV, which is dependent on JNK activation (Yin et al., 2012). Furthermore, PRRSV infection also activates IRE1 phosphorylation, one of the arms of the unfolded protein responses (UPR, also known as ER stress responses), which may contribute to JNK-mediated apoptosis (Huo et al., 2013). These studies have shown that JNK signaling pathway might play a vital role in PRRSV-induced apoptosis of host cells.

3.1.4. Escape from immune responses utilizing miRNAs

MicroRNAs (miRNAs) are a class of small non-coding RNA molecules (~21–23 nt) that regulate gene expression post-transcriptionally through degradation of mRNAs or inhibition of translation (Krol et al., 2010). These molecules have emerged as critical gene regulators in complex life, including differentiation, development, cellular proliferation and death, immune responses and virus infection. Recent studies have provided compelling evidence that multiple miRNAs including miR-146a, miR-155 (Vigorito et al., 2013), miR-21, miR-23b (Zhu et al., 2012), miR-126 (Agudo et al., 2014), miRNA-181a (Ebert et al., 2009; Li et al., 2007a; Xie et al., 2013; Zietara et al., 2013), and miR-17–92 clusters (Jiang et al., 2011; Khan et al., 2013; Wu et al., 2012) are involved in the regulation of innate and adaptive immune response, including the release of inflammatory mediators, the development and activation of B and T cells and the proliferation of monocytes and neutrophils (Contreras and Rao, 2012; David, 2010; Lindsay, 2008; Nahid et al., 2011; O'Neill et al., 2011). Not surprisingly, during viral infection, host miRNAs can affect viral replication by regulating host immune responses to generate a less permissive environment for viral replications. In the case of miR-155, it is induced during viral infection and inhibits virus infection by positively regulating innate immune responses (Su et al., 2011). For example, during VSV infection, miR-155 is induced to inhibit VSV infection by enhancing type I interferon responses via targeting suppressor of cytokine signaling 1 (SOCS1) (Wang et al., 2010). Similarly, miR-155 induced by Japanese encephalitis virus (JEV) infection in microglial cells suppresses JEV replication through positively modulating innate immune responses by targetingSH2-domain-containing inositol-5-phosphatase 1 (SHIP1) (Pareek et al., 2014; Thounaojam et al., 2014). In addition, as a critical modulator of $CD8^+$ T cell responses, miR-155 is induced in $CD8^+$ T cells in responses to lymphocytic choriomeningitis virus (LCMV) infection and is critical for the antiviral $CD8^+$ T cell responses to acute and chronic LCMV infection (Dudda et al., 2013).

On the other side, many viruses have evolved to induce miRNAs, which act as negative regulators of immune responses to facilitate viral infection. Different from miR-155, miR-146a is reported to facilitate virus replication by dampening interferon induction by targeting TNFR-associated factor 6 (TRAF6) and IL-1R-associated kinase 1 (IRAK1). A previous report has shown that Enterovirus 71 (EV71)-induced miR-146a facilitates viral infection and pathogenesis by suppressing IFN production (Ho et al., 2014). Similar to miR-146a, miR-21 is demonstrated to be induced by HCV and contributes to evasion of host immune system by targeting MyD88 and IRAK1. It's worth noting that virus-derived miRNAs actively participate in evasion of immune responses to facilitate viral replication (Cullen, 2013; Skalsky and Cullen, 2010). For example, a human herpesvirus miRNA attenuates interferon signaling and help maintain viral latency by targeting IKKε (Liang et al., 2011). Another example is the human torque teno virus (TTV), which encodes a microRNA (TTV-tth8-miR-T1) that inhibits interferon signaling by targeting N-myc and STAT interactor (NMI), a positive modulator of STAT signaling pathways (Kincaid et al., 2013).

During PRRSV infection, many miRNAs are found to be altered, suggesting that miRNAs might be involved in PRRSV infection (Hicks et al., 2013). Although little is known about the exact role of miRNAs in PRRSV pathogenesis, two recent studies may give some hints. miR-125b is found to reduce PRRSV replication by decreasing NF-κB expression through stabilizing κB-RAS2, which serves as a negative regulator of NF-κB. Moreover, miR-125b is down-regulated by PRRSV infection and this may be a strategy for PRRSV to evade host immune responses by inhibiting the NF-κB signaling pathway (Wang et al., 2013a). In our recently published paper, we demonstrate that miR-23, a miRNA induced by poly(I:C), can suppress PRRSV replication by promoting the expression of type I IFNs. PRRSV infection suppresses the expression of poly(I:C)-induced miR-23, implying that this antagonism might be a strategy used by PRRSV to evade the miRNA-mediated immune responses induced in TLR3 pathway (Zhang et al., 2014). Notably, during PRRSV infection, the well-characterized immune-modulator miR-146a is up-regulated. Since miR-146a is a negative regulator of immune

responses, it is likely that the up-regulation of miR-146a might facilitate viral infection by suppressing IFN production. Moreover, as type I IFN production and signaling is severely crippled during PRRSV infection, it is important to investigate whether any of the miRNAs is involved in the evasion of host immune responses by regulating the production or signaling of IFNs. And this clarification might help us understand the pathogenesis of PRRSV.

3.2. Escape from adaptive immunity

3.2.1. Impairing antigen presentation

Dendritic cells (DCs), the most potent of the prominent antigen presenting cells (APCs), play important roles in the generation of T-cell responses and the maintenance of immune responses (Banchereau and Steinman, 1998; Steinman, 2012). Upon PRRSV infection, these cells are activated and undergo maturation, and then migrate to the lung-draining lymph nodes where they present viral epitopes to naïve T cells (Freigang et al., 2005). This process results in proliferation and differentiation of naïve T cells into effector cells, triggering adaptive immune responses. To impair immune responses, PRRSV have evolved defense mechanisms to inhibit the antigen presentation function of DCs. The reduced expression of MHC class I and II molecules are observed in PRRSV-infected monocyte-derived dendritic cells (Mo-DCs) (Wang et al., 2007) and bone marrow-derived dendritic cells (BM-DCs) (Chang et al., 2008; Peng et al., 2009; Weesendorp et al., 2013). The expression of co-stimulatory molecule CD80/86 varies possibly because of using different strains. Another strategy used by PRRSV to counter DCs function is the induction of cell death via both apoptosis and necrosis mechanisms (Rodriguez-Gomez et al., 2013). The down-regulation of the cell surface molecules and cell death of DCs lead to a failure in the onset of an efficient adaptive immunity. T cell responses are reported to appear at 4–8 weeks and $CD4^+$- and $CD8^+$-T cells remain low and constant after infection, indicating that cell-mediated immunity (CMI) is transient and delayed in PRRSV infection (Bautista and Molitor, 1997; Feng et al., 2002; Lopez Fuertes et al., 1999; Xiao et al., 2004).

3.2.2. Activation of immunosuppressive regulatory T cells

Immunosuppressive regulatory T cells (Tregs) are responsible for balancing the immune responses and maintaining immune homeostasis by controlling or inhibiting the functions of immunocompetent effector cells. Tregs are divided into natural and inducible Tregs, which are developed in the thymus or generated in the periphery from naive $CD4^+$ T cells, respectively (Belkaid, 2007; Miyara and Sakaguchi, 2007). Based on the cytokines they produce, inducible Tregs can be classified into three subsets that are described in humans and mice, including Treg 1 cells (Tr1) which secrete IL-10, T helper 3 cells (Th3) which secrete TGF-β, and $CD8^+$ Tregs (Belkaid, 2007; Shevach, 2006). In pigs, two main Tregs are identified and described as $CD4^+CD8^-CD25^+Foxp3^+$ and $CD4^+CD8^+CD25^+Foxp3^+$ (Kaser et al., 2008).

Tregs are commonly recognized as a key contributor in regulating the magnitude of the host immune responses to viral infection, thus protect against excessive inflammation and tissue damage. However, many viruses including human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), and hepatitis C virus (HCV) induce proliferation and activation of Tregs to escape the immune responses and establish persistent infection (Kinter et al., 2004; Smyk-Pearson et al., 2008; Vahlenkamp et al., 2005; Voo et al., 2005). In recent years, several studies have also revealed that PRRSV activates Tregs both in vitro and in vivo (Cecere et al., 2012; LeRoith et al., 2011; Manickam et al., 2013; Wongyanin et al., 2010). Silva-Campa and colleagues have shown that Tregs are induced by PRRSV-infected DCs, which is dependent on the production of TGFβ (Silva-Campa et al., 2009). Subsequently, they have identified that PRRSV infection induces the proliferation of Tregs with the phenotype $CD4^+CD8^+CD25^+Foxp3^{high}$ (Silva-Campa et al., 2012). This team has also demonstrated that American genotype PRRSV strains are able to induce Tregs and up-regulate TGFβ expression, but neither TGFβ nor Tregs are induced by European genotype PRRSV (Silva-Campa et al., 2010). Furthermore, up-regulation of IL-10 gene expression and induction of Tregs have been observed when using N protein-pulsed porcine Mo-DCs, indicating that N protein might play a significant role in the induction of IL-10 and Tregs (Wongyanin et al., 2012). The ability of PRRSV to induce Tregs likely contributes to the persistence in host and may be in favor of secondary infection.

3.2.3. Antibody-dependent enhancement (ADE)

The humoral immune responses to PRRSV have been studied. In PRRSV-infected pigs, specific IgM antibodies are detectable in serum by day 5–7 post-infection (PI), and reach a peak at day 14 PI and then decline (Yoon et al., 1995). Concentrations of IgG antibodies reach a peak at 21–49 days PI (Loemba et al., 1996; Vezina et al., 1996). At the early stage of infection, these antibodies are directed against N, M, GP5 and nsp2 proteins (de Lima et al., 2006). However, these rapid antibody responses do not correspond to neutralizing antibodies (NAs). NAs appear by 4 weeks PI or later and are mainly directed against GP5 protein, which contains the major neutralizing epitopes located in the N-terminal ectodomain of GP5 (Ostrowski et al., 2002; Plagemann, 2004; Yoon et al., 1994). NAs play an important role in the protection against PRRSV infection, but maintain at low levels (Lopez and Osorio, 2004). The inefficient humoral immune responses cannot eliminate virus from host.

Besides the common CD163 receptor-dependent mechanism of cellular attachment (Welch and Calvert, 2010), PRRSV relies on antiviral antibodies for its entry into host cells, such as macrophages and monocytes (Yoon et al., 1996). This phenomenon is known as antibody-dependent enhancement (ADE). Previous studies have shown that the yield of progeny PRRSV significantly increases in PAMs in the presence of diluted anti-PRRSV antisera, and viremia is much severer in pigs injected with sub-neutralizing antibodies before virus infection than that in animals injected with normal IgG, indicating that ADE facilitates the entry of PRRSV into target cells through Fc receptor-mediated endocytosis (Halstead et al., 2010; Mateu and Diaz, 2008). Qiao et al. have found that the enhancement of PRRSV infection is inhibited by anti-porcine FcγRII antibody when MARC-poFcγRII cells and PAMs are infected in the presence of anti-PRRSV antibody (Qiao et al., 2011). This result suggests that poFcγRIIb, an inhibitory FcγR, mediates ADE of PRRSV infection.

In addition, ADE also interferes with innate signaling responses. Previous study has indicated that pretreatment with FcγRIIb-specific IgG up-regulates the transcriptional levels of IFNα and TNFα, but down-regulates IL-10 in PRRSV-infected PAMs (Zhang et al., 2012). The expression of TNFα and IFNβ is suppressed in the presence of anti-PRRSV antibodies. Moreover, qPCR analysis shows that mRNA levels of transcriptional factors, NF-κB, IRF1 and IRF3 are greatly inhibited in PRRSV-Ab-infected macrophages (Bao et al., 2013). Thus, these results demonstrate that ADE signaling alters innate antiviral responses by modulating the expression of key antiviral factors.

4. Implications for vaccine development

Both killed and modified live PRRS vaccines have been developed soon after PRRS outbreak. PRRS killed virus vaccine is safe but induces poor immune responses and has poor protection against either homologous or heterologous PRRSV (Charerntantanakul, 2012). On the other hand, commercial PRRS modified-live virus

(MLV) vaccine has been widely used and shown some efficacy in reducing viremia and virus shedding (Murtaugh et al., 2002). However, MLV elicits delayed humoral and cell-mediated immunity and has only partial protective efficacy against genetically heterologous PRRSV strains (Charerntantanakul, 2012). Thus, development of effective PRRSV vaccine must consider and conquer the high genetic and antigenic variability of PRRSV and its ability to manipulate the host immune system.

MLVs can be developed by deletion and transformation of the key virulence factors using reverse genetics techniques. Genetic manipulations of influenza viruses that express truncated forms of the NS1 protein, a strong inhibitor of type I IFNs (Hale et al., 2010), are shown to be defective in suppressing IFN responses and induce reduction of replication in animal models (Richt and Garcia-Sastre, 2009). The recombinant mouse hepatitis virus (MHV) lacking nsp1 gene induces robust type I IFN and is strongly attenuated in mice (Zust et al., 2007). As outlined above, PRRSV has evolved a number of strategies to modulate host immune responses, especially antiviral type I IFNs. Several PRRSV proteins (nsp1, nsp2, nsp4, nsp11 and N) are involved in inhibiting type I IFN responses. Previous study reveals that MLV nsp1β has no effect on mediation of KPNA1 degradation, and does not inhibit IFN-mediated signaling, which is in contrast with VR2332 nsp1β because of the difference in amino acids (Wang et al., 2013b). Thus, recombinant PRRSV that changes the immune-regulatory function of these proteins to restore IFN responses may provide a strategy for the development of PRRSV vaccines.

PRRSV has the ability to impair antigen presentation function of APCs. APC-target strategies can be used to strengthen the efficacy of vaccines against PRRSV. Fusion of antigens with cytotoxic-T-lymphocyte-associated protein 4 (CTLA4) enhances immune responses to a model DNA vaccine, because CTLA4 binds to APCs (Boyle et al., 1998). In our study, we construct a fusion expression plasmid expressing CTLA4 and PRRSV GP5, which contains T-cell epitopes and induces neutralizing antibodies. Mice immunized with the fusion expression plasmids show more production of neutralizing antibodies (NAs), IFNγ, IL-4, and the lymphocyte proliferation activity than mice immunized with GP5 expression plasmids, indicating that CTLA4 fused with GP5 can enhance GP5 immunogenicity (Wang et al., 2013c).

For RNA virus, antigenic variability and rapid replication are also effective ways to evade host immune responses. To attenuate virus replication, de-optimization of codon pair bias is a valid strategy (Coleman et al., 2008; Mueller et al., 2010). Ni et al. have attenuated PRRSV by codon-pair deoptimized GP5 gene using synthetic attenuated virus engineering (SAVE) (Ni et al., 2014). In our recent study, nsp2 and nsp9 genes of HP-PRRSV have been codon-pair deoptimized and the recombinants HP-PRRSV HV-nsp9^{min} and HV-nsp29^{min} are rescued (unpublished data). These recombinant viruses are remarkably attenuated in PAMs and in vivo. Furthermore, vaccination with HV-nsp29^{min} has ability to protect pigs from lethal challenge with wild-type HP-PRRSV isolates. Our results suggest that the codon pair bias de-optimized HV-nsp29^{min} has the potential to be used as a live vaccine candidate against HP-PRRSV.

5. Conclusion

Strategies of immune evasion and modulation used by PRRSV affect both innate and adaptive immune responses. In infected cells, PRRSV sequesters itself to limit PRRs detection, suppresses type I IFN production and signaling, manipulates the cytokine responses and modulates apoptosis. PRRSV structural protein (N) and nonstructional proteins (nsp1, nsp2, nsp4 and nsp11) play significant roles in attenuating signaling through the IFN induction and JAK/STAT pathway. In addition, PRRSV evolves mechanisms to inhibit the process of antigen presentation and induce proliferation and activation of Tregs, causing deficiency of subsequent adaptive immune responses. The effect of ADE also facilitates the entry and propagation of PRRSV. Even though the fact that PRRSV and its viral proteins interfere with host immune responses has been described, the exact molecular mechanisms and structural bases for the antagonism between viral components and host key factors are still unclear and require extensive investigations. These insights will help us understand the PRRSV pathogenesis and develop more effective and broadly protective vaccines.

Acknowledgements

The writing of this review was supported by the State Key Laboratory of Agrobiotechnology (Grant 2013SKLAB1-5 and 2014SKLAB1-3) and the Research Fund for the Doctoral Program of Higher Education of China (Grant No. 20130008110028).

References

Agudo, J., Ruzo, A., Tung, N., Salmon, H., Leboeuf, M., Hashimoto, D., Becker, C., Garrett-Sinha, L.A., Baccarini, A., Merad, M., Brown, B.D., 2014. The miR-126-VEGFR2 axis controls the innate response to pathogen-associated nucleic acids. Nat. Immunol. 15 (1), 54–62.

Akira, S., Uematsu, S., Takeuchi, O., 2006. Pathogen recognition and innate immunity. Cell 124 (4), 783–801.

Albina, E., 1997. Epidemiology of porcine reproductive and respiratory syndrome (PRRS): an overview. Vet. Microbiol. 55 (1–4), 309–316.

Albina, E., Carrat, C., Charley, B., 1998. Interferon-alpha response to swine arterivirus (PoAV), the porcine reproductive and respiratory syndrome virus. J. Interf. Cytokine Res.: Off. J. Int. Soc. Interf. Cytokine Res. 18 (7), 485–490.

Albina, E., Madec, F., Cariolet, R., Torrison, J., 1994. Immune-response and persistence of the porcine reproductive and respiratory syndrome virus in infected-pigs and farm units. Vet. Rec. 134 (22), 567–573.

Allende, R., Lewis, T.L., Lu, Z., Rock, D.L., Kutish, G.F., Ali, A., Doster, A.R., Osorio, F.A., 1999. North American and European porcine reproductive and respiratory syndrome viruses differ in non-structural protein coding regions. J. Gen. Virol. 80 (Pt. 2), 307–315.

Banadyga, L., Veugelers, K., Campbell, S., Barry, M., 2009. The Fowlpox virus BCL-2 homologue, FPV039, interacts with activated bax and a discrete subset of BH3-only proteins to inhibit apoptosis. J. Virol. 83 (14), 7085–7098.

Banchereau, J., Steinman, R.M., 1998. Dendritic cells and the control of immunity. Nature 392 (6673), 245–252.

Bao, D., Wang, R., Qiao, S., Wan, B., Wang, Y., Liu, M., Shi, X., Guo, J., Zhang, G., 2013. Antibody-dependent enhancement of PRRSV infection down-modulates TNF-alpha and IFN-beta transcription in macrophages. Vet. Immunol. Immunopathol. 156 (1–2), 128–134.

Bautista, E.M., Molitor, T.W., 1997. Cell-mediated immunity to porcine reproductive and respiratory syndrome virus in swine. Viral Immunol. 10 (2), 83–94.

Belkaid, Y., 2007. Regulatory T cells and infection: a dangerous necessity. Nat. Rev. Immunol. 7 (11), 875–888.

Belsham, G.J., McInerney, G.M., Ross-Smith, N., 2000. Foot-and-mouth disease virus 3C protease induces cleavage of translation initiation factors eIF4A and eIF4G within infected cells. J. Virol. 74 (1), 272–280.

Beura, L.K., Sarkar, S.N., Kwon, B., Subramaniam, S., Jones, C., Pattnaik, A.K., Osorio, F.A., 2010. Porcine reproductive and respiratory syndrome virus nonstructural protein 1beta modulates host innate immune response by antagonizing IRF3 activation. J. Virol. 84 (3), 1574–1584.

Beyer, J., Fichtner, D., Schirrmeier, H., Polster, U., Weiland, E., Wege, H., 2000. Porcine reproductive and respiratory syndrome virus (PRRSV): kinetics of infection in lymphatic organs and lung. J. Vet. Med. B 47 (1), 9–25.

Bilodeau, R., Dea, S., Sauvageau, R.A., Martineau, G.P., 1991. 'Porcine reproductive and respiratory syndrome' in Quebec. Vet. Rec. 129 (5), 102–103.

Bode, J.G., Ludwig, S., Ehrhardt, C., Albrecht, U., Erhardt, A., Schaper, F., Heinrich, P.C., Haussinger, D., 2003. IFN-alpha antagonistic activity of HCV core protein involves induction of suppressor of cytokine signaling-3. FASEB J. 17 (3), 488–490.

Boyle, J.S., Brady, J.L., Lew, A.M., 1998. Enhanced response to a DNA vaccine encoding a fusion antigen that is directed to sites of immune induction. Nature 392 (6674), 408–411.

Budihardjo, I., Oliver, H., Lutter, M., Luo, X., Wang, X., 1999. Biochemical pathways of caspase activation during apoptosis. Annu. Rev. Cell Dev. Biol. 15, 269–290.

Cai, Q., Guo, Y., Xiao, B., Banerjee, S., Saha, A., Lu, J., Glisovic, T., Robertson, E.S., 2011. Epstein-Barr virus nuclear antigen 3C stabilizes Gemin3 to block p53-mediated apoptosis. PLoS Pathog. 7 (12), e1002418.

Calzada-Nova, G., Schnitzlein, W.M., Husmann, R.J., Zuckermann, F.A., 2011. North American porcine reproductive and respiratory syndrome viruses inhibit type I interferon production by plasmacytoid dendritic cells. J. Virol. 85 (6), 2703–2713.

Cavanagh, D., 1997. Nidovirales: a new order comprising Coronaviridae and Arteriviridae. Arch. Virol. 142 (3), 629–633.

Cecere, T.E., Todd, S.M., Leroith, T., 2012. Regulatory T cells in arterivirus and coronavirus infections: do they protect against disease or enhance it? Viruses 4 (5), 833–846.
Chang, H.C., Peng, Y.T., Chang, H.L., Chaung, H.C., Chung, W.B., 2008. Phenotypic and functional modulation of bone marrow-derived dendritic cells by porcine reproductive and respiratory syndrome virus. Vet. Microbiol. 129 (3–4), 281–293.
Charerntantanakul, W., 2012. Porcine reproductive and respiratory syndrome virus vaccines: immunogenicity, efficacy and safety aspects. World J. Virol. 1 (1), 23–30.
Chen, Z., Lawson, S., Sun, Z., Zhou, X., Guan, X., Christopher-Hennings, J., Nelson, E.A., Fang, Y., 2010. Identification of two auto-cleavage products of nonstructural protein 1 (nsp1) in porcine reproductive and respiratory syndrome virus infected cells: nsp1 function as interferon antagonist. Virology 398 (1), 87–97.
Chen, Z., Li, M., He, Q., Du, J., Zhou, L., Ge, X., Guo, X., Yang, H., 2014. The amino acid at residue 155 in nonstructural protein 4 of porcine reproductive and respiratory syndrome virus contributes to its inhibitory effect for interferon-beta transcription in vitro. Virus Res. 189C, 226–234.
Cho, J.G., Dee, S.A., 2006. Porcine reproductive and respiratory syndrome virus. Theriogenology 66 (3), 655–662.
Coleman, J.R., Papamichail, D., Skiena, S., Futcher, B., Wimmer, E., Mueller, S., 2008. Virus attenuation by genome-scale changes in codon pair bias. Science 320 (5884), 1784–1787.
Conti, P., Kempuraj, D., Kandere, K., Di Gioacchino, M., Barbacane, R.C., Castellani, M.L., Felaco, M., Boucher, W., Letourneau, R., Theoharides, T.C., 2003. IL-10, an inflammatory/inhibitory cytokine, but not always. Immunol. Lett. 86 (2), 123–129.
Contreras, J., Rao, D.S., 2012. MicroRNAs in inflammation and immune responses. Leukemia 26 (3), 404–413.
Costers, S., Lefebvre, D.J., Delputte, P.L., Nauwynck, H.J., 2008. Porcine reproductive and respiratory syndrome virus modulates apoptosis during replication in alveolar macrophages. Arch. Virol. 153 (8), 1453–1465.
Cullen, B.R., 2013. MicroRNAs as mediators of viral evasion of the immune system. Nat. Immunol. 14 (3), 205–210.
D'Cunha, J., Ramanujam, S., Wagner, R.J., Witt, P.L., Knight Jr., E., Borden, E.C., 1996. In vitro and in vivo secretion of human ISG15, an IFN-induced immunomodulatory cytokine. J. Immunol. 157 (9), 4100–4108.
David, M., 2010. Interferons and microRNAs. J. Interf. Cytokine Res.: Off. J. Int. Soc. Interf. Cytokine Res. 30 (11), 825–828.
DCunha, J., Knight, E., Haas, A.L., Truitt, R.L., Borden, E.C., 1996. Immunoregulatory properties of ISG15, an interferon-induced cytokine. Proc. Natl. Acad. Sci. U. S. A. 93 (1), 211–215.
de Lima, M., Pattnaik, A.K., Flores, E.F., Osorio, F.A., 2006. Serologic marker candidates identified among B-cell linear epitopes of Nsp2 and structural proteins of a North American strain of porcine reproductive and respiratory syndrome virus. Virology 353 (2), 410–421.
den Boon, J.A., Faaberg, K.S., Meulenberg, J.J., Wassenaar, A.L., Plagemann, P.G., Gorbalenya, A.E., Snijder, E.J., 1995. Processing and evolution of the N-terminal region of the arterivirus replicase ORF1a protein: identification of two papainlike cysteine proteases. J. Virol. 69 (7), 4500–4505.
Deng, L., Wang, C., Spencer, E., Yang, L., Braun, A., You, J., Slaughter, C., Pickart, C., Chen, Z.J., 2000. Activation of the IkappaB kinase complex by TRAF6 requires a dimeric ubiquitin-conjugating enzyme complex and a unique polyubiquitin chain. Cell 103 (2), 351–361.
Diebold, S.S., Kaisho, T., Hemmi, H., Akira, S., Reis e Sousa, C., 2004. Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. Science 303 (5663), 1529–1531.
Dokland, T., 2010. The structural biology of PRRSV. Virus Res. 154 (1–2), 86–97.
Done, S.H., Paton, D.J., 1995. Porcine reproductive and respiratory syndrome: clinical disease, pathology and immunosuppression. Vet. Rec. 136 (2), 32–35.
Dudda, J.C., Salaun, B., Ji, Y., Palmer, D.C., Monnot, G.C., Merck, E., Boudousquie, C., Utzschneider, D.T., Escobar, T.M., Perret, R., Muljo, S.A., Hebeisen, M., Rufer, N., Zehn, D., Donda, A., Restifo, N.P., Held, W., Gattinoni, L., Romero, P., 2013. MicroRNA-155 is required for effector CD8+ T cell responses to virus infection and cancer. Immunity 38 (4), 742–753.
Ebert, P.J., Jiang, S., Xie, J., Li, Q.J., Davis, M.M., 2009. An endogenous positively selecting peptide enhances mature T cell responses and becomes an autoantigen in the absence of microRNA miR-181a. Nat. Immunol. 10 (11), 1162–1169.
Edwards, M.R., Slater, L., Johnston, S.L., 2007. Signalling pathways mediating type I interferon gene expression. Microbes Infect./Inst. Pasteur 9 (11), 1245–1251.
Fang, Y., Fang, L., Wang, Y., Lei, Y., Luo, R., Wang, D., Chen, H., Xiao, S., 2012a. Porcine reproductive and respiratory syndrome virus nonstructural protein 2 contributes to NF-kappaB activation. Virol. J. 9, 83.
Fang, Y., Snijder, E.J., 2010. The PRRSV replicase: exploring the multifunctionality of an intriguing set of nonstructural proteins. Virus Res. 154 (1–2), 61–76.
Fang, Y., Treffers, E.E., Li, Y., Tas, A., Sun, Z., van der Meer, Y., de Ru, A.H., van Veelen, P.A., Atkins, J.F., Snijder, E.J., Firth, A.E., 2012b. Efficient −2 frameshifting by mammalian ribosomes to synthesize an additional arterivirus protein. Proc. Natl. Acad. Sci. U. S. A. 109 (43), E2920–E2928.
Feng, W.H., Tompkins, M.B., Xu, J.S., Brown, T.T., Laster, S.M., Zhang, H.X., McCaw, M.B., 2002. Thymocyte and peripheral blood T lymphocyte subpopulation changes in piglets following in utero infection with porcine reproductive and respiratory syndrome virus. Virology 302 (2), 363–372.
Flores-Mendoza, L., Silva-Campa, E., Resendiz, M., Osorio, F.A., Hernandez, J., 2008. Porcine reproductive and respiratory syndrome virus infects mature porcine dendritic cells and up-regulates interleukin-10 production. Clin. Vaccine Immunol. 15 (4), 720–725.
Freigang, S., Probst, H.C., van den Broek, M., 2005. DC infection promotes antiviral CTL priming: the 'Winkelried' strategy. Trends Immunol. 26 (1), 13–18.
Frias-Staheli, N., Giannakopoulos, N.V., Kikkert, M., Taylor, S.L., Bridgen, A., Paragas, J., Richt, J.A., Rowland, R.R., Schmaljohn, C.S., Lenschow, D.J., Snijder, E.J., Garcia-Sastre, A., Virgin, H.W.t., 2007. Ovarian tumor domain-containing viral proteases evade ubiquitin- and ISG15-dependent innate immune responses. Cell Host Microbe 2 (6), 404–416.
Gomez-Laguna, J., Salguero, F.J., Pallares, F.J., Fernandez de Marco, M., Barranco, I., Ceron, J.J., Martinez-Subiela, S., Van Reeth, K., Carrasco, L., 2010. Acute phase response in porcine reproductive and respiratory syndrome virus infection. Comp. Immunol. Microbiol. Infect. Dis. 33 (6), e51–e58.
Hale, B.G., Albrecht, R.A., Garcia-Sastre, A., 2010. Innate immune evasion strategies of influenza viruses. Future Microbiol. 5 (1), 23–41.
Halstead, S.B., Mahalingam, S., Marovich, M.A., Ubol, S., Mosser, D.M., 2010. Intrinsic antibody-dependent enhancement of microbial infection in macrophages: disease regulation by immune complexes. Lancet Infect. Dis. 10 (10), 712–722.
Ho, B.C., Yu, I.S., Lu, L.F., Rudensky, A., Chen, H.Y., Tsai, C.W., Chang, Y.L., Wu, C.T., Chang, L.Y., Shih, S.R., Lin, S.W., Lee, C.N., Yang, P.C., Yu, S.L., 2014. Inhibition of miR-146a prevents enterovirus-induced death by restoring the production of type I interferon. Nature Commun. 5, 3344.
Hoebe, K., Janssen, E., Beutler, B., 2004. The interface between innate and adaptive immunity. Nat. Immunol. 5 (10), 971–974.
Honda, K., Takaoka, A., Taniguchi, T., 2006. Type I interferon [corrected] gene induction by the interferon regulatory factor family of transcription factors. Immunity 25 (3), 349–360.
Hotchkiss, R.S., Nicholson, D.W., 2006. Apoptosis and caspases regulate death and inflammation in sepsis. Nat. Rev. Immunol. 6 (11), 813–822.
Hou, J., Wang, L., He, W., Zhang, H., Feng, W.H., 2012a. Highly pathogenic porcine reproductive and respiratory syndrome virus impairs LPS- and poly(I:C)-stimulated tumor necrosis factor-alpha release by inhibiting ERK signaling pathway. Virus Res. 167 (1), 106–111.
Hou, J., Wang, L., Quan, R., Fu, Y., Zhang, H., Feng, W.H., 2012b. Induction of interleukin-10 is dependent on p38 mitogen-activated protein kinase pathway in macrophages infected with porcine reproductive and respiratory syndrome virus. Virol. J. 9, 165.
Huang, C., Zhang, Q., Guo, X.K., Yu, Z.B., Xu, A.T., Tang, J., Feng, W.H., 2014. Porcine reproductive and respiratory syndrome virus nonstructural protein 4 antagonizes IFNbeta expression by targeting NEMO. J. Virol. 88 (18), 10934–10945.
Huang, Y.W., Meng, X.J., 2010. Novel strategies and approaches to develop the next generation of vaccines against porcine reproductive and respiratory syndrome virus (PRRSV). Virus Res. 154 (1–2), 141–149.
Huo, Y., Fan, L., Yin, S., Dong, Y., Guo, X., Yang, H., Hu, H., 2013. Involvement of unfolded protein response, p53 and Akt in modulation of porcine reproductive and respiratory syndrome virus-mediated JNK activation. Virology 444 (1–2), 233–240.
Hicks, J.A., Yoo, D., Liu, H.C., 2013. Characterization of the microRNAome in porcine reproductive and respiratory syndrome virus infected macrophages. PLOS ONE 8 (12), e82054.
Jan, J.T., Chen, B.H., Ma, S.H., Liu, C.I., Tsai, H.P., Wu, H.C., Jiang, S.Y., Yang, K.D., Shaio, M.F., 2000. Potential dengue virus-triggered apoptotic pathway in human neuroblastoma cells: arachidonic acid, superoxide anion, and NF-kappa B are sequentially involved. J. Virol. 74 (18), 8680–8691.
Jiang, S., Li, C., Olive, V., Lykken, E., Feng, F., Sevilla, J., Wan, Y., He, L., Li, Q.J., 2011. Molecular dissection of the miR-17-92 cluster's critical dual roles in promoting Th1 responses and preventing inducible Treg differentiation. Blood 118 (20), 5487–5497.
Jiang, Z., Zhou, X., Michal, J.J., Wu, X.L., Zhang, L., Zhang, M., Ding, B., Liu, B., Manoranjan, V.S., Neill, J.D., Harhay, G.P., Kehrli Jr., M.E., Miller, L.C., 2013. Reactomes of porcine alveolar macrophages infected with porcine reproductive and respiratory syndrome virus. PLOS ONE 8 (3), e59229.
Kabelitz, D., Medzhitov, R., 2007. Innate immunity – cross-talk with adaptive immunity through pattern recognition receptors and cytokines. Curr. Opin. Immunol. 19 (1), 1–3.
Kaser, T., Gerner, W., Hammer, S.E., Patzl, M., Saalmuller, A., 2008. Detection of Foxp3 protein expression in porcine T lymphocytes. Vet. Immunol. Immunopathol. 125 (1–2), 92–101.
Kawai, T., Akira, S., 2006. Innate immune recognition of viral infection. Nat. Immunol. 7 (2), 131–137.
Kawai, T., Akira, S., 2010. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat. Immunol. 11 (5), 373–384.
Kawai, T., Takahashi, K., Sato, S., Coban, C., Kumar, H., Kato, H., Ishii, K.J., Takeuchi, O., Akira, S., 2005. IPS-1, an adaptor triggering RIG-I- and Mda5-mediated type I interferon induction. Nat. Immunol. 6 (10), 981–988.
Khan, A.A., Penny, L.A., Yuzefpolskiy, Y., Sarkar, S., Kalia, V., 2013. MicroRNA-17∼92 regulates effector and memory CD8 T-cell fates by modulating proliferation in response to infections. Blood 121 (22), 4473–4483.
Kim, O., Sun, Y., Lai, F.W., Song, C., Yoo, D., 2010. Modulation of type I interferon induction by porcine reproductive and respiratory syndrome virus and degradation of CREB-binding protein by non-structural protein 1 in MARC-145 and HeLa cells. Virology 402 (2), 315–326.
Kincaid, R.P., Burke, J.M., Cox, J.C., de Villiers, E.M., Sullivan, C.S., 2013. A human torque teno virus encodes a microRNA that inhibits interferon signaling. PLoS Pathog. 9 (12), e1003818.
Kinter, A.L., Hennessey, M., Bell, A., Kern, S., Lin, Y., Daucher, M., Planta, M., McGlaughlin, M., Jackson, R., Ziegler, S.F., Fauci, A.S., 2004. CD25(+)CD4(+) regulatory T cells from the peripheral blood of asymptomatic HIV-infected individuals

regulate CD4(+) and CD8(+) HIV-specific T cell immune responses in vitro and are associated with favorable clinical markers of disease status. J. Exp. Med. 200 (3), 331–343.
Knoops, K., Kikkert, M., Worm, S.H., Zevenhoven-Dobbe, J.C., van der Meer, Y., Koster, A.J., Mommaas, A.M., Snijder, E.J., 2008. SARS-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. PLoS Biol. 6 (9), e226.
Kroese, M.V., Zevenhoven-Dobbe, J.C., Bos-de Ruijter, J.N., Peeters, B.P., Meulenberg, J.J., Cornelissen, L.A., Snijder, E.J., 2008. The nsp1alpha and nsp1 papain-like autoproteinases are essential for porcine reproductive and respiratory syndrome virus RNA synthesis. J. Gen. Virol. 89 (Pt. 2), 494–499.
Krol, J., Loedige, I., Filipowicz, W., 2010. The widespread regulation of microRNA biogenesis, function and decay. Nat. Rev. Genet. 11 (9), 597–610.
Kuwahara, H., Nunoya, T., Tajima, M., Kato, A., Samejima, T., 1994. An outbreak of porcine reproductive and respiratory syndrome in Japan. J. Vet. Med. Sci./Jpn. Soc. Vet. Sci. 56 (5), 901–909.
Labarque, G., Van Gucht, S., Nauwynck, H., Van Reeth, K., Pensaert, M., 2003. Apoptosis in the lungs of pigs infected with porcine reproductive and respiratory syndrome virus and associations with the production of apoptogenic cytokines. Vet. Res. 34 (3), 249–260.
Lei, X., Xiao, X., Xue, Q., Jin, Q., He, B., Wang, J., 2013. Cleavage of interferon regulatory factor 7 by enterovirus 71 3C suppresses cellular responses. J. Virol. 87 (3), 1690–1698.
LeRoith, T., Hammond, S., Todd, S.M., Ni, Y., Cecere, T., Pelzer, K.D., 2011. A modified live PRRSV vaccine and the pathogenic parent strain induce regulatory T cells in pigs naturally infected with Mycoplasma hyopneumoniae. Vet. Immunol. Immunopathol. 140 (3–4), 312–316.
Li, H., Zheng, Z., Zhou, P., Zhang, B., Shi, Z., Hu, Q., Wang, H., 2010. The cysteine protease domain of porcine reproductive and respiratory syndrome virus nonstructural protein 2 antagonizes interferon regulatory factor 3 activation. J. Gen. Virol. 91 (Pt. 12), 2947–2958.
Li, M.L., Hsu, T.A., Chen, T.C., Chang, S.C., Lee, J.C., Chen, C.C., Stollar, V., Shih, S.R., 2002. The 3C protease activity of enterovirus 71 induces human neural cell apoptosis. Virology 293 (2), 386–395.
Li, Q.J., Chau, J., Ebert, P.J., Sylvester, G., Min, H., Liu, G., Braich, R., Manoharan, M., Soutschek, J., Skare, P., Klein, L.O., Davis, M.M., Chen, C.Z., 2007a. miR-181a is an intrinsic modulator of T cell sensitivity and selection. Cell 129 (1), 147–161.
Li, Y., Treffers, E.E., Napthine, S., Tas, A., Zhu, L., Sun, Z., Bell, S., Mark, B.L., van Veelen, P.A., van Hemert, M.J., Firth, A.E., Brierley, I., Snijder, E.J., Fang, Y., 2014. Transactivation of programmed ribosomal frameshifting by a viral protein. Proc. Natl. Acad. Sci. U. S. A. 111 (21), E2172–E2181.
Li, Y.F., Wang, X.L., Bo, K.T., Wang, X.W., Tang, B., Yang, B.S., Jiang, W., Jiang, P., 2007b. Emergence of a highly pathogenic porcine reproductive and respiratory syndrome virus in the Mid-Eastern region of China. Vet. J. 174 (3), 577–584.
Liang, D., Gao, Y., Lin, X., He, Z., Zhao, Q., Deng, Q., Lan, K., 2011. A human herpesvirus miRNA attenuates interferon signaling and contributes to maintenance of viral latency by targeting IKKepsilon. Cell Res. 21 (5), 793–806.
Lindsay, M.A., 2008. microRNAs and the immune response. Trends Immunol. 29 (7), 343–351.
Loemba, H.D., Mounir, S., Mardassi, H., Archambault, D., Dea, S., 1996. Kinetics of humoral immune response to the major structural proteins of the porcine reproductive and respiratory syndrome virus. Arch. Virol. 141 (3–4), 751–761.
Loo, Y.M., Gale Jr., M., 2011. Immune signaling by RIG-I-like receptors. Immunity 34 (5), 680–692.
Lopez-Fuertes, L., Campos, E., Domenech, N., Ezquerra, A., Castro, J.M., Dominguez, J., Alonso, F., 2000. Porcine reproductive and respiratory syndrome (PRRS) virus down-modulates TNF-alpha production in infected macrophages. Virus Res. 69 (1), 41–46.
Lopez Fuertes, L., Domenech, N., Alvarez, B., Ezquerra, A., Dominguez, J., Castro, J.M., Alonso, F., 1999. Analysis of cellular immune response in pigs recovered from porcine respiratory and reproductive syndrome infection. Virus Res. 64 (1), 33–42.
Lopez, O.J., Osorio, F.A., 2004. Role of neutralizing antibodies in PRRSV protective immunity. Vet. Immunol. Immunopathol. 102 (3), 155–163.
Ma, Z., Wang, Y., Zhao, H., Xu, A.T., Wang, Y., Tang, J., Feng, W.H., 2013. Porcine reproductive and respiratory syndrome virus nonstructural protein 4 induces apoptosis dependent on its 3C-like serine protease activity. PloS one 8 (7), e69387.
Makarova, K.S., Aravind, L., Koonin, E.V., 2000. A novel superfamily of predicted cysteine proteases from eukaryotes, viruses and *Chlamydia pneumoniae*. Trends Biochem. Sci. 25 (2), 50–52.
Manickam, C., Dwivedi, V., Patterson, R., Papenfuss, T., Renukaradhya, G.J., 2013. Porcine reproductive and respiratory syndrome virus induces pronounced immune modulatory responses at mucosal tissues in the parental vaccine strain VR2332 infected pigs. Vet. Microbiol. 162 (1), 68–77.
Mateu, E., Diaz, I., 2008. The challenge of PRRS immunology. Vet. J. 177 (3), 345–351.
Medigeshi, G.R., Lancaster, A.M., Hirsch, A.J., Briese, T., Lipkin, W.I., DeFilippis, V., Fruh, M., Mason, P.W., Nikolich-Zugich, J., Nelson, J.A., 2007. West Nile virus infection activates the unfolded protein response, leading to CHOP induction and apoptosis. J. Virol. 81 (20), 10849–10860.
Metz, G.E., Serena, M.S., Abeya, M.M., Dulbecco, A.B., Massone, A., Diaz, S., Echeverria, M.G., 2014. Equine arteritis virus gP5 protein induces apoptosis in cultured insect cells. Virus Res. 183, 81–84.
Miller, L.C., Laegreid, W.W., Bono, J.L., Chitko-McKown, C.G., Fox, J.M., 2004. Interferon type I response in porcine reproductive and respiratory syndrome virus-infected MARC-145 cells. Arch. Virol 149 (12), 2453–2463.
Miyara, M., Sakaguchi, S., 2007. Natural regulatory T cells: mechanisms of suppression. Trends Mol. Med. 13 (3), 108–116.
Moore, K.W., de Waal Malefyt, R., Coffman, R.L., O'Garra, A., 2001. Interleukin-10 and the interleukin-10 receptor. Annu. Rev. Immunol. 19, 683–765.
Morrison, R.B., Collins, J.E., Harris, L., Christianson, W.T., Benfield, D.A., Chladek, D.W., Gorcyca, D.E., Joo, H.S., 1992. Serologic evidence incriminating a recently isolated virus (ATCC VR-2332) as the cause of swine infertility and respiratory syndrome (SIRS). J. Vet. Diagn. Invest.: Off. Publ. Am. Assoc. Vet. Lab. Diagn. Inc. 4 (2), 186–188.
Mueller, S., Coleman, J.R., Papamichail, D., Ward, C.B., Nimnual, A., Futcher, B., Skiena, S., Wimmer, E., 2010. Live attenuated influenza virus vaccines by computer-aided rational design. Nat. Biotechnol. 28 (7), 723–726.
Mukherjee, A., Morosky, S.A., Delorme-Axford, E., Dybdahl-Sissoko, N., Oberste, M.S., Wang, T., Coyne, C.B., 2011. The coxsackievirus B 3C protease cleaves MAVS and TRIF to attenuate host type I interferon and apoptotic signaling. PLoS Pathog. 7 (3), e1001311.
Murtaugh, M.P., Xiao, Z., Zuckermann, F., 2002. Immunological responses of swine to porcine reproductive and respiratory syndrome virus infection. Viral Immunol. 15 (4), 533–547.
Nahid, M.A., Satoh, M., Chan, E.K., 2011. MicroRNA in TLR signaling and endotoxin tolerance. Cell. Mol. Immunol. 8 (5), 388–403.
Natoli, G., Costanzo, A., Guido, F., Moretti, F., Levrero, M., 1998. Apoptotic, non-apoptotic, and anti-apoptotic pathways of tumor necrosis factor signalling. Biochem. Pharmacol. 56 (8), 915–920.
Nedialkova, D.D., Ulferts, R., van den Born, E., Lauber, C., Gorbalenya, A.E., Ziebuhr, J., Snijder, E.J., 2009. Biochemical characterization of arterivirus nonstructural protein 11 reveals the nidovirus-wide conservation of a replicative endoribonuclease. J. Virol. 83 (11), 5671–5682.
Neumann, E.J., Kliebenstein, J.B., Johnson, C.D., Mabry, J.W., Bush, E.J., Seitzinger, A.H., Green, A.L., Zimmerman, J.J., 2005. Assessment of the economic impact of porcine reproductive and respiratory syndrome on swine production in the United States. J. Am. Vet. Med. Assoc. 227 (3), 385–392.
Ni, Y.Y., Zhao, Z., Opriessnig, T., Subramaniam, S., Zhou, L., Cao, D., Cao, Q., Yang, H., Meng, X.J., 2014. Computer-aided codon-pairs deoptimization of the major envelope GP5 gene attenuates porcine reproductive and respiratory syndrome virus. Virology 450–451, 132–139.
O'Neill, L.A., Sheedy, F.J., McCoy, C.E., 2011. MicroRNAs: the fine-tuners of Toll-like receptor signalling. Nature reviews. Immunology 11 (3), 163–175.
Oshiumi, H., Matsumoto, M., Funami, K., Akazawa, T., Seya, T., 2003. TICAM-1, an adaptor molecule that participates in Toll-like receptor 3-mediated interferon-beta induction. Nat. Immunol. 4 (2), 161–167.
Ostrowski, M., Galeota, J.A., Jar, A.M., Platt, K.B., Osorio, F.A., Lopez, O.J., 2002. Identification of neutralizing and nonneutralizing epitopes in the porcine reproductive and respiratory syndrome virus GP5 ectodomain. J. Virol. 76 (9), 4241–4250.
Ouyang, W., Rutz, S., Crellin, N.K., Valdez, P.A., Hymowitz, S.G., 2011. Regulation and functions of the IL-10 family of cytokines in inflammation and disease. Annu. Rev. Immunol. 29, 71–109.
Overend, C., Mitchell, R., He, D., Rompato, G., Grubman, M.J., Garmendia, A.E., 2007. Recombinant swine beta interferon protects swine alveolar macrophages and MARC-145 cells from infection with Porcine reproductive and respiratory syndrome virus. J. Gen. Virol. 88 (Pt. 3), 925–931.
Pareek, S., Roy, S., Kumari, B., Jain, P., Banerjee, A., Vrati, S., 2014. MiR-155 induction in microglial cells suppresses Japanese encephalitis virus replication and negatively modulates innate immune responses. J. Neuroinflam. 11, 97.
Patel, D., Nan, Y., Shen, M., Ritthipichai, K., Zhu, X., Zhang, Y.J., 2010. Porcine reproductive and respiratory syndrome virus inhibits type I interferon signaling by blocking STAT1/STAT2 nuclear translocation. J. Virol. 84 (21), 11045–11055.
Pauli, E.K., Schmolke, M., Wolff, T., Viemann, D., Roth, J., Bode, J.G., Ludwig, S., 2008. Influenza A virus inhibits type I IFN signaling via NF-kappa B-dependent induction of SOCS-3 expression. PLoS Pathog. 4 (11).
Pedersen, K.W., van der Meer, Y., Roos, N., Snijder, E.J., 1999. Open reading frame 1a-encoded subunits of the arterivirus replicase induce endoplasmic reticulum-derived double-membrane vesicles which carry the viral replication complex. J. Virol. 73 (3), 2016–2026.
Pejsak, Z., Stadejek, T., Markowska-Daniel, I., 1997. Clinical signs and economic losses caused by porcine reproductive and respiratory syndrome virus in a large breeding farm. Vet. Microbiol. 55 (1–4), 317–322.
Peng, Y.T., Chaung, H.C., Chang, H.L., Chang, H.C., Chung, W.B., 2009. Modulations of phenotype and cytokine expression of porcine bone marrow-derived dendritic cells by porcine reproductive and respiratory syndrome virus. Vet. Microbiol. 136 (3–4), 359–365.
Perlman, S., Netland, J., 2009. Coronaviruses post-SARS: update on replication and pathogenesis. Nat. Rev. Microbiol. 7 (6), 439–450.
Pichlmair, A., Reis e Sousa, C., 2007. Innate recognition of viruses. Immunity 27 (3), 370–383.
Pitha-Rowe, I., Hassel, B.A., Dmitrovsky, E., 2004. Involvement of UBE1L in ISG15 conjugation during retinoid-induced differentiation of acute promyelocytic leukemia. J. Biol. Chem. 279 (18), 18178–18187.
Plagemann, P.G., 2004. The primary GP5 neutralization epitope of North American isolates of porcine reproductive and respiratory syndrome virus. Vet. Immunol. Immunopathol. 102 (3), 263–275.
Plagemann, P.G., Moennig, V., 1992. Lactate dehydrogenase-elevating virus, equine arteritis virus, and simian hemorrhagic fever virus: a new group of positive-strand RNA viruses. Adv. Virus Res. 41, 99–192.

Pujhari, S., Baig, T.T., Zakhartchouk, A.N., 2014. Potential role of porcine reproductive and respiratory syndrome virus structural protein GP2 in apoptosis inhibition. BioMed Res. Int. 2014, 160505.
Qiao, S.L., Jiang, Z.Z., Tian, X.H., Wang, R., Xing, G.X., Wan, B., Bao, D.K., Liu, Y.H., Hao, H.F., Guo, J.Q., Zhang, G.P., 2011. Porcine Fc gamma RIIb mediates enhancement of porcine reproductive and respiratory syndrome virus (PRRSV) infection. PLoS ONE 6 (12).
Rathinam, V.A.K., Vanaja, S.K., Fitzgerald, K.A., 2012. Regulation of inflammasome signaling. Nat. Immunol. 13 (4), 332–333.
Richt, J.A., Garcia-Sastre, A., 2009. Attenuated influenza virus vaccines with modified NS1 proteins. Curr. Top. Microbiol. Immunol. 333, 177–195.
Rodriguez-Gomez, I.M., Gomez-Laguna, J., Carrasco, L., 2013. Impact of PRRSV on activation and viability of antigen presenting cells. World J. Virol. 2 (4), 146–151.
Rossow, K.D., 1998. Porcine reproductive and respiratory syndrome. Vet. Pathol. 35 (1), 1–20.
Rowland, R.R., Kervin, R., Kuckleburg, C., Sperlich, A., Benfield, D.A., 1999. The localization of porcine reproductive and respiratory syndrome virus nucleocapsid protein to the nucleolus of infected cells and identification of a potential nucleolar localization signal sequence. Virus Res. 64 (1), 1–12.
Rowland, R.R., Lawson, S., Rossow, K., Benfield, D.A., 2003. Lymphoid tissue tropism of porcine reproductive and respiratory syndrome virus replication during persistent infection of pigs originally exposed to virus in utero. Vet. Microbiol. 96 (3), 219–235.
Rudin, C.M., Thompson, C.B., 1997. Apoptosis and disease: regulation and clinical relevance of programmed cell death. Annu. Rev. Med. 48, 267–281.
Sabat, R., Grutz, G., Warszawska, K., Kirsch, S., Witte, E., Wolk, K., Geginat, J., 2010. Biology of interleukin-10. Cytokine Growth Factor Rev. 21 (5), 331–344.
Sadler, A.J., Williams, B.R., 2008. Interferon-inducible antiviral effectors. Nat. Rev. Immunol. 8 (7), 559–568.
Sagong, M., Lee, C., 2011. Porcine reproductive and respiratory syndrome virus nucleocapsid protein modulates interferon-β production by inhibiting IRF3 activation in immortalized porcine alveolar macrophages. Arch. Virol. 156 (12), 2187–2195.
Saraiva, M., O'Garra, A., 2010. The regulation of IL-10 production by immune cells. Nat. Rev. Immunol. 10 (3), 170–181.
Schoggins, J.W., Rice, C.M., 2011. Interferon-stimulated genes and their antiviral effector functions. Curr. Opin. Virol. 1 (6), 519–525.
Schoggins, J.W., Wilson, S.J., Panis, M., Murphy, M.Y., Jones, C.T., Bieniasz, P., Rice, C.M., 2011. A diverse range of gene products are effectors of the type I interferon antiviral response. Nature 472 (7344), 481–485.
Seth, R.B., Sun, L., Ea, C.K., Chen, Z.J., 2005. Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF-kappaB and IRF 3. Cell 122 (5), 669–682.
Shen, L., Zhang, X., Hu, D., Feng, T., Li, H., Lu, Y., Huang, J., 2013. Hepatitis B virus X (HBx) play an anti-apoptosis role in hepatic progenitor cells by activating Wnt/beta-catenin pathway. Mol. Cell. Biochem. 383 (1–2), 213–222.
Shevach, E.M., 2006. From vanilla to 28 flavors: multiple varieties of T regulatory cells. Immunity 25 (2), 195–201.
Shi, X., Wang, L., Li, X., Zhang, G., Guo, J., Zhao, D., Chai, S., Deng, R., 2011. Endoribonuclease activities of porcine reproductive and respiratory syndrome virus nsp11 was essential for nsp11 to inhibit IFN-beta induction. Mol. Immunol. 48 (12–13), 1568–1572.
Silva-Campa, E., Cordoba, L., Fraile, L., Flores-Mendoza, L., Montoya, M., Hernandez, J., 2010. European genotype of porcine reproductive and respiratory syndrome (PRRSV) infects monocyte-derived dendritic cells but does not induce Treg cells. Virology 396 (2), 264–271.
Silva-Campa, E., Flores-Mendoza, L., Resendiz, M., Pinelli-Saavedra, A., Mata-Haro, V., Mwangi, W., Hernandez, J., 2009. Induction of T helper 3 regulatory cells by dendritic cells infected with porcine reproductive and respiratory syndrome virus. Virology 387 (2), 373–379.
Silva-Campa, E., Mata-Haro, V., Mateu, E., Hernandez, J., 2012. Porcine reproductive and respiratory syndrome virus induces CD4 + CD8 + CD25 + Foxp3+ regulatory T cells (Tregs). Virology 430 (1), 73–80.
Skalsky, R.L., Cullen, B.R., 2010. Viruses, microRNAs, and host interactions. Annu. Rev. Microbiol. 64, 123–141.
Smith, C.A., Farrah, T., Goodwin, R.G., 1994. The TNF receptor superfamily of cellular and viral proteins: activation, costimulation, and death. Cell 76 (6), 959–962.
Smyk-Pearson, S., Golden-Mason, L., Klarquist, J., Burton Jr., J.R., Tester, I.A., Wang, C.C., Culbertson, N., Vandenbark, A.A., Rosen, H.R., 2008. Functional suppression by FoxP3 + CD4 + CD25(high) regulatory T cells during acute hepatitis C virus infection. J. Infect. Dis. 197 (1), 46–57.
Snijder, E.J., Meulenberg, J.J., 1998. The molecular biology of arteriviruses. J. Gen. Virol. 79 (Pt. 5), 961–979.
Snijder, E.J., Wassenaar, A.L., van Dinten, L.C., Spaan, W.J., Gorbalenya, A.E., 1996. The arterivirus nsp4 protease is the prototype of a novel group of chymotrypsin-like enzymes, the 3C-like serine proteases. J. Biol. Chem. 271 (9), 4864–4871.
Song, C., Krell, P., Yoo, D., 2010. Nonstructural protein 1alpha subunit-based inhibition of NF-kappaB activation and suppression of interferon-beta production by porcine reproductive and respiratory syndrome virus. Virology 407 (2), 268–280.
Song, S., Bi, J., Wang, D., Fang, L., Zhang, L., Li, F., Chen, H., Xiao, S., 2013. Porcine reproductive and respiratory syndrome virus infection activates IL-10 production through NF-kappaB and p38 MAPK pathways in porcine alveolar macrophages. Dev. Comp. Immunol. 39 (3), 265–272.
Stark, G.R., Darnell Jr., J.E., 2012. The JAK-STAT pathway at twenty. Immunity 36 (4), 503–514.
Steinman, R.M., 2012. Decisions about dendritic cells: past, present, and future. Annu. Rev. Immunol. 30 (30), 1–22.
Stevenson, G.W., Vanalstine, W.G., Kanitz, C.L., Keffaber, K.K., 1993. Endemic porcine reproductive and respiratory syndrome virus-infection of nursery pigs in 2 swine herds without current reproductive failure. J. Vet. Diagn. Invest. 5 (3), 432–434.
Su, C., Hou, Z., Zhang, C., Tian, Z., Zhang, J., 2011. Ectopic expression of microRNA-155 enhances innate antiviral immunity against HBV infection in human hepatoma cells. Virol. J. 8, 354.
Suarez, P., 2000. Ultrastructural pathogenesis of the PRRS virus. Vet. Res. 31 (1), 47–55.
Subramaniam, S., Kwon, B., Beura, L.K., Kuszynski, C.A., Pattnaik, A.K., Osorio, F.A., 2010. Porcine reproductive and respiratory syndrome virus non-structural protein 1 suppresses tumor necrosis factor-alpha promoter activation by inhibiting NF-kappaB and Sp1. Virology 406 (2), 270–279.
Sun, Y., Li, D., Giri, S., Prasanth, S.G., Yoo, D., 2014. Differential host cell gene expression and regulation of cell cycle progression by nonstructural protein 11 of porcine reproductive and respiratory syndrome virus. BioMed Res. Int. 2014, 430508.
Sun, Z., Chen, Z., Lawson, S.R., Fang, Y., 2010. The cysteine protease domain of porcine reproductive and respiratory syndrome virus nonstructural protein 2 possesses deubiquitinating and interferon antagonism functions. J. Virol. 84 (15), 7832–7846.
Sun, Z., Li, Y., Ransburgh, R., Snijder, E.J., Fang, Y., 2012. Nonstructural protein 2 of porcine reproductive and respiratory syndrome virus inhibits the antiviral function of interferon-stimulated gene 15. J. Virol. 86 (7), 3839–3850.
Suradhat, S., Thanawongnuwech, R., 2003. Upregulation of interleukin-10 gene expression in the leukocytes of pigs infected with porcine reproductive and respiratory syndrome virus. J. Gen. Virol. 84 (Pt. 10), 2755–2760.
Suradhat, S., Thanawongnuwech, R., Poovorawan, Y., 2003. Upregulation of IL-10 gene expression in porcine peripheral blood mononuclear cells by porcine reproductive and respiratory syndrome virus. J. Gen. Virol. 84, 453–459.
Tait, S.W.G., Green, D.R., 2010. Mitochondria and cell death: outer membrane permeabilization and beyond. Nat. Rev. Mol. Cell Biol. 11 (9), 621–632.
Takahashi, K., Kawai, T., Kumar, H., Sato, S., Yonehara, S., Akira, S., 2006. Roles of caspase-8 and caspase-10 in innate immune responses to double-stranded RNA. J. Immunol. 176 (8), 4520–4524.
Takaoka, A., Yanai, H., 2006. Interferon signalling network in innate defence. Cell. Microbiol. 8 (6), 907–922.
Takeuchi, O., Akira, S., 2008. MDA5/RIG-I and virus recognition. Curr. Opin. Immunol. 20 (1), 17–22.
Takeuchi, O., Akira, S., 2010. Pattern recognition receptors and inflammation. Cell 140 (6), 805–820.
Tenoever, B.R., Maniatis, T., 2006. Parallel pathways of virus recognition. Immunity 24 (5), 510–512.
Thanawongnuwech, R., Thacker, E.L., 2003. Interleukin-10, interleukin-12, and interferon-gamma levels in the respiratory tract following mycoplasma hyopneumoniae and PRRSV infection in pigs. Viral Immunol. 16 (3), 357–367.
Theofilopoulos, A.N., Baccala, R., Beutler, B., Kono, D.H., 2005. Type I interferons (alpha/beta) in immunity and autoimmunity. Annu. Rev. Immunol. 23, 307–336.
Thomson, B.J., 2001. Viruses and apoptosis. Int. J. Exp. Pathol. 82 (2), 65–76.
Thounaojam, M.C., Kundu, K., Kaushik, D.K., Swaroop, S., Mahadevan, A., Shankar, S.K., Basu, A., 2014. MicroRNA 155 regulates Japanese encephalitis virus-induced inflammatory response by targeting Src homology 2-containing inositol phosphatase 1. J. Virol. 88 (9), 4798–4810.
Tian, K., Yu, X., Zhao, T., Feng, Y., Cao, Z., Wang, C., Hu, Y., Chen, X., Hu, D., Tian, X., Liu, D., Zhang, S., Deng, X., Ding, Y., Yang, L., Zhang, Y., Xiao, H., Qiao, M., Wang, B., Hou, L., Wang, X., Yang, X., Kang, L., Sun, M., Jin, P., Wang, S., Kitamura, Y., Yan, J., Gao, G.F., 2007. Emergence of fatal PRRSV variants: unparalleled outbreaks of atypical PRRS in China and molecular dissection of the unique hallmark. PLoS ONE 2 (6), e526.
Tian, X., Lu, G., Gao, F., Peng, H., Feng, Y., Ma, G., Bartlam, M., Tian, K., Yan, J., Hilgenfeld, R., Gao, G.F., 2009. Structure and cleavage specificity of the chymotrypsin-like serine protease (3CLSP/nsp4) of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV). J. Mol. Biol. 392 (4), 977–993.
Toews, G.B., 2001. Cytokines and the lung. Eur. Respir. J. 34 (Suppl.), 3s–17s.
Vahlenkamp, T.W., Tompkins, M.B., Tompkins, W.A., 2005. The role of CD4 + CD25+ regulatory T cells in viral infections. Vet. Immunol. Immunopathol. 108 (1–2), 219–225.
Vezina, S.A., Loemba, H., Fournier, M., Dea, S., Archambault, D., 1996. Antibody production and blastogenic response in pigs experimentally infected with porcine reproductive and respiratory syndrome virus. Rev. Can. Rech. Vet. 60 (2), 94–99.
Vigorito, E., Kohlhaas, S., Lu, D., Leyland, R., 2013. miR-155: an ancient regulator of the immune system. Immunol. Rev. 253 (1), 146–157.
Voo, K.S., Peng, G., Guo, Z., Fu, T., Li, Y., Frappier, L., Wang, R.F., 2005. Functional characterization of EBV-encoded nuclear antigen 1-specific CD4+ helper and regulatory T cells elicited by in vitro peptide stimulation. Cancer Res. 65 (4), 1577–1586.
Wang, C., Deng, L., Hong, M., Akkaraju, G.R., Inoue, J., Chen, Z.J., 2001. TAK1 is a ubiquitin-dependent kinase of MKK and IKK. Nature 412 (6844), 346–351.
Wang, D., Cao, L., Xu, Z., Fang, L., Zhong, Y., Chen, Q., Luo, R., Chen, H., Li, K., Xiao, S., 2013a. MiR-125b reduces porcine reproductive and respiratory syndrome virus replication by negatively regulating the NF-kappaB pathway. PLOS ONE 8 (2), e55838.
Wang, G., He, Y., Tu, Y., Liu, Y., Zhou, E.M., Han, Z., Jiang, C., Wang, S., Shi, W., Cai, X., 2014. Comparative analysis of apoptotic changes in peripheral immune organs

and lungs following experimental infection of piglets with highly pathogenic and classical porcine reproductive and respiratory syndrome virus. Virol. J. 11, 2.
Wang, G., Song, T., Yu, Y., Liu, Y., Shi, W., Wang, S., Rong, F., Dong, J., Liu, H., Cai, X., Zhou, E.M., 2011. Immune responses in piglets infected with highly pathogenic porcine reproductive and respiratory syndrome virus. Vet. Immunol. Immunopathol. 142 (3–4), 170–178.
Wang, P., Hou, J., Lin, L., Wang, C., Liu, X., Li, D., Ma, F., Wang, Z., Cao, X., 2010. Inducible microRNA-155 feedback promotes type I IFN signaling in antiviral innate immunity by targeting suppressor of cytokine signaling 1. J. Immunol. 185 (10), 6226–6233.
Wang, R., Nan, Y., Yu, Y., Zhang, Y.J., 2013b. Porcine reproductive and respiratory syndrome virus Nsp1beta inhibits interferon-activated JAK/STAT signal transduction by inducing karyopherin-alpha1 degradation. J. Virol. 87 (9), 5219–5228.
Wang, X., Eaton, M., Mayer, M., Li, H., He, D., Nelson, E., Christopher-Hennings, J., 2007. Porcine reproductive and respiratory syndrome virus productively infects monocyte-derived dendritic cells and compromises their antigen-presenting ability. Arch. Virol 152 (2), 289–303.
Wang, Y., Zhao, H., Ma, Z., Wang, Y., Feng, W.H., 2013c. CTLA4 mediated targeting enhances immunogenicity against PRRSV in a DNA prime/killed virus boost strategy. Vet. Immunol. Immunopathol. 154 (3–4), 121–128.
Weesendorp, E., Stockhofe-Zurwieden, N., Popma-De Graaf, D.J., Fijten, H., Rebel, J.M., 2013. Phenotypic modulation and cytokine profiles of antigen presenting cells by European subtype 1 and 3 porcine reproductive and respiratory syndrome virus strains in vitro and in vivo. Vet. Microbiol. 167 (3–4), 638–650.
Wei, C., Huang, Z., Sun, L., Xie, J., Chen, Y., Zhang, M., Zhang, C., Qi, H., Qi, W., Ning, Z., Yuan, L., Wang, H., Zhang, L., Zhang, G., 2013. Expression and antibody preparation of GP5a gene of porcine reproductive and respiratory syndrome virus. Indian J. Microbiol. 53 (3), 370–375.
Welch, S.K., Calvert, J.G., 2010. A brief review of CD163 and its role in PRRSV infection. Virus Res. 154 (1–2), 98–103.
Weng, K.F., Li, M.L., Hung, C.T., Shih, S.R., 2009. Enterovirus 71 3C protease cleaves a novel target CstF-64 and inhibits cellular polyadenylation. PLoS Pathog. 5 (9), e1000593.
Wensvoort, G., Terpstra, C., Pol, J.M., ter Laak, E.A., Bloemraad, M., de Kluyver, E.P., Kragten, C., van Buiten, L., den Besten, A., Wagenaar, F., et al., 1991. Mystery swine disease in the Netherlands: the isolation of Lelystad virus. Vet. Q. 13 (3), 121–130.
Wills, R.W., Zimmerman, J.J., Yoon, K.J., Swenson, S.L., McGinley, M.J., Hill, H.T., Platt, K.B., Christopher-Hennings, J., Nelson, E.A., 1997. Porcine reproductive and respiratory syndrome virus: a persistent infection. Vet. Microbiol. 55 (1–4), 231–240.
Wong, J.J.Y., Pung, Y.F., Sze, N.S.K., Chin, K.C., 2006. HERC5 is an IFN-induced HECT-type E3 protein ligase that mediates type I IFN-induced ISGylation of protein targets. Proc. Natl. Acad. Sci. U. S. A. 103 (28), 10735–10740.
Wongyanin, P., Buranapraditkul, S., Yoo, D., Thanawongnuwech, R., Roth, J.A., Suradhat, S., 2012. Role of porcine reproductive and respiratory syndrome virus nucleocapsid protein in induction of interleukin-10 and regulatory T-lymphocytes (Treg). J. Gen. Virol. 93 (Pt. 6), 1236–1246.
Wongyanin, P., Buranapraditkun, S., Chokeshai-Usaha, K., Thanawonguwech, R., Suradhat, S., 2010. Induction of inducible CD4 + CD25 + Foxp3+ regulatory T lymphocytes by porcine reproductive and respiratory syndrome virus (PRRSV). Vet. Immunol. Immunopathol. 133 (2–4), 170–182.
Wu, T., Wieland, A., Araki, K., Davis, C.W., Ye, L., Hale, J.S., Ahmed, R., 2012. Temporal expression of microRNA cluster miR-17-92 regulates effector and memory CD8+ T-cell differentiation. Proc. Natl. Acad. Sci. U. S. A. 109 (25), 9965–9970.
Xiao, Z., Batista, L., Dee, S., Halbur, P., Murtaugh, M.P., 2004. The level of virus-specific T-cell and macrophage recruitment in porcine reproductive and respiratory syndrome virus infection in pigs is independent of virus load. J. Virol. 78 (11), 5923–5933.
Xie, W., Li, Z., Li, M., Xu, N., Zhang, Y., 2013. miR-181a and inflammation: miRNA homeostasis response to inflammatory stimuli in vivo. Biochem. Biophys. Res. Commun. 430 (2), 647–652.
Xu, L.G., Wang, Y.Y., Han, K.J., Li, L.Y., Zhai, Z., Shu, H.B., 2005. VISA is an adapter protein required for virus-triggered IFN-beta signaling. Mol. Cell 19 (6), 727–740.
Yan, N., Chen, Z.J., 2012. Intrinsic antiviral immunity. Nat. Immunol. 13 (3), 214–222.
Yin, S., Huo, Y., Dong, Y., Fan, L., Yang, H., Wang, L., Ning, Y., Hu, H., 2012. Activation of c-Jun NH(2)-terminal kinase is required for porcine reproductive and respiratory syndrome virus-induced apoptosis but not for virus replication. Virus Res. 166 (1–2), 103–108.
Yokota, S., Yokosawa, N., Okabayashi, T., Suzutani, T., Miura, S., Jimbow, K., Fujii, N., 2004. Induction of suppressor of cytokine signaling-3 by herpes simplex virus type 1 contributes to inhibition of the interferon signaling pathway. J. Virol. 78 (12), 6282–6286.
Yoo, D., Wootton, S.K., Li, G., Song, C., Rowland, R.R., 2003. Colocalization and interaction of the porcine arterivirus nucleocapsid protein with the small nucleolar RNA-associated protein fibrillarin. J. Virol. 77 (22), 12173–12183.
Yoon, I.J., Joo, H.S., Goyal, S.M., Molitor, T.W., 1994. A modified serum neutralization test for the detection of antibody to porcine reproductive and respiratory syndrome virus in swine sera. J. Vet. Diagn. Invest. 6 (3), 289–292.
Yoon, K.J., Wu, L.L., Zimmerman, J.J., Hill, H.T., Platt, K.B., 1996. Antibody-dependent enhancement (ADE) of porcine reproductive and respiratory syndrome virus (PRRSV) infection in pigs. Viral Immunol. 9 (1), 51–63.
Yoon, K.J., Zimmerman, J.J., Swenson, S.L., McGinley, M.J., Eernisse, K.A., Brevik, A., Rhinehart, L.L., Frey, M.L., Hill, H.T., Platt, K.B., 1995. Characterization of the humoral immune response to porcine reproductive and respiratory syndrome (PRRS) virus infection. J. Vet. Diagn. Invest.: Off. Publ. Am. Assoc. Vet. Lab. Diagn. Inc. 7 (3), 305–312.
Yun, S.I., Lee, Y.M., 2013. Overview: replication of porcine reproductive and respiratory syndrome virus. J. Microbiol. 51 (6), 711–723.
Zhang, Q., Guo, X.K., Gao, L., Huang, C., Li, N., Jia, X., Liu, W., Feng, W.H., 2014. MicroRNA-23 inhibits PRRSV replication by directly targeting PRRSV RNA and possibly by upregulating type I interferons. Virology 450–451, 182–195.
Zhang, Y., Zhou, Y., Yang, Q., Mu, C., Duan, E., Chen, J., Yang, M., Xia, P., Cui, B., 2012. Ligation of Fc gamma receptor IIB enhances levels of antiviral cytokine in response to PRRSV infection in vitro. Vet. Microbiol. 160 (3–4), 473–480.
Zhao, C., Beaudenon, S.L., Kelley, M.L., Waddell, M.B., Yuan, W.M., Schulman, B.A., Huibregtse, J.M., Krug, R.M., 2004. The UbcH8 ubiquitin E2 enzyme is also the E2 enzyme for ISG15, an IFN-alpha/beta-induced ubiquitin-like protein. Proc. Natl. Acad. Sci. U. S. A. 101 (20), 7578–7582.
Zhao, C., Collins, M.N., Hsiang, T.Y., Krug, R.M., 2013. Interferon-induced ISG15 pathway: an ongoing virus-host battle. Trends Microbiol. 21 (4), 181–186.
Zhou, Y., Bai, J., Li, Y., Wang, X., Wang, X., Jiang, P., 2012. Suppression of immune responses in pigs by nonstructural protein 1 of porcine reproductive and respiratory syndrome virus. Rev. Can. Rech. Vet. 76 (4), 255–260.
Zhu, S., Pan, W., Song, X., Liu, Y., Shao, X., Tang, Y., Liang, D., He, D., Wang, H., Liu, W., Shi, Y., Harley, J.B., Shen, N., Qian, Y., 2012. The microRNA miR-23b suppresses IL-17-associated autoimmune inflammation by targeting TAB2, TAB3 and IKK-alpha. Nat. Med. 18 (7), 1077–1086.
Ziebuhr, J., Snijder, E.J., Gorbalenya, A.E., 2000. Virus-encoded proteinases and proteolytic processing in the Nidovirales. J. Gen. Virol. 81 (Pt. 4), 853–879.
Zietara, N., Lyszkiewicz, M., Witzlau, K., Naumann, R., Hurwitz, R., Langemeier, J., Bohne, J., Sandrock, I., Ballmaier, M., Weiss, S., Prinz, I., Krueger, A., 2013. Critical role for miR-181a/b-1 in agonist selection of invariant natural killer T cells. Proc. Natl. Acad. Sci. U. S. A. 110 (18), 7407–7412.
Zust, R., Cervantes-Barragan, L., Kuri, T., Blakqori, G., Weber, F., Ludewig, B., Thiel, V., 2007. Coronavirus non-structural protein 1 is a major pathogenicity factor: implications for the rational design of coronavirus vaccines. PLoS Pathog. 3 (8), 1062–1072.