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REVIEW

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Current research progress on the viral immune evasion mechanisms of African swine fever

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Abstract

African swine fever (ASF), caused by the ASF virus (ASFV), is an acute, severe, and highly contagious infectious disease in domestic pigs and wild boars. Domestic pigs infected with a virulent ASFV strain can have morbidity and mortality rates of up to 100%. The epidemic of ASF has caused serious economic losses to the global pig industry. Currently, there is no safe and effective vaccine or specific drug for treating ASF. Therefore, ASFV still poses a great threat to pig factories. ASFV is a double-stranded DNA virus with a complex icosahedral multilayer structure. The ASFV genome contains 150–170 open reading frames (ORFs) that encode 150–200 proteins. Some ASFV-encoded proteins are involved in virus invasion, genome replication, DNA repair, and virion formation. Some ASFV proteins execute immunomodulatory functions by regulating the host antiviral innate immune response. Accumulating studies have shown that the immunomodulatory functions of ASFV genes are closely related to the virulence and pathogenicity of ASFV isolates. This review summarizes the research advances on ASFV immune evasion mechanisms in African swine fever patients and provides new insights for developing attenuated live vaccine candidates to prevent and control ASF.

Keywords African swine fever, Immunoregulatory gene, Live attenuated vaccines, Antiviral innate immune responses

Introduction

African swine fever (ASF) is a virulent, hemorrhagic infectious disease caused by African swine fever virus (ASFV), which infects farmed pigs and wild boars. ASFV is characterized by very high lethality; domestic pigs infected with virulent ASFV strains have a mortality rate as high as 100% (Schafer et al. 2022). According to the official website of the World Organization for Animal Health (WOAH), a total of 5,882 cases of ASF, including 4,218 cases involving wild boar, occurred in 26 countries in 2023. In addition, 422,500 live pigs were slaughtered, demonstrating the difficulty of preventing and controlling ASF outbreaks. The global pig industry is currently facing major ASF issues due to a lack of safe and effective vaccines and commercial treatments. ASF is characterized by different clinical manifestations, including peracute/hyperacute, acute, subacute, and chronic manifestations (Tulman et al. 2009; Gallardo et al. 2018), which depend not only on the genetic background of the ASFV isolates but also on the genetic background of the host (Walczak et al. 2020).

African swine fever virus (ASFV) is a large enveloped double-stranded DNA (dsDNA) virus and the sole member of the *Asfarviridae* family that belongs to the category of nucleocytoplasmic large DNA viruses (NCLDVs) (Karki et al. 2021). ASFV particles are composed of

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complex, multilayered structures consisting of a genome-containing nucleoid, a core shell with thick proteins, an inner lipid envelope, a capsid, and an external envelope from the inside out (Wang et al. 2019). Mature virions acquire an external lipid envelope by budding through the plasma membrane. The ASFV genome varies in length from 170 to 194 kb and contains 150-170 open reading frames (ORFs), which encode more than 150 proteins in ASFV-infected cells (Perez-Nunez et al. 2019). The main functions of ASFV-encoded proteins include the regulation of viral replication (Dixon et al. 2013; Simoes et al. 2019; Urbano and Ferreira 2020), DNA repair (Maciejewski et al. 2001; Lamarche et al. 2005; Lamarche et al. 2006; Sampoli Benitez et al. 2008; Redrejo-Rodriguez et al. 2013), transcription (Rodriguez and Salas 2013; Cackett et al. 2020), virus assembly (Wang et al. 2019; Heath et al. 2001; Zhou et al. 2022a), and immune evasion (Correia et al. 2013; Dixon et al. 2019; He et al. 2022). The activities of approximately half of the ASFV genes are currently unknown and require further investigation.

ASFV infects porcine alveolar macrophages (PAMs) and mononuclear macrophages, which include particular tissue macrophages and reticular epithelial cell lineages (Pan et al. 1988). Previous studies have shown that ASFV can enter target cells by interacting with receptors on the cell membrane (Galindo et al. 1997), a process that is also associated with clathrin-mediated endocytosis (Chen et al. 2023a) or macropinocytosis. Then, the inner viral envelope fuses with the secondary endosome, and the viral genome is released into the cytoplasm (Matamoros et al. 2020).

Recently, several ASFV proteins have been confirmed to be multifunctional proteins (Zhou et al. 2022a; Huang et al. 2023a; Ye et al. 2023; Li et al. 2021a; Li et al. 2021b). These compounds exhibit immunomodulatory effects, which are critical for viral immune evasion and ASFV pathogenicity. Notably, the pathogenicity of ASFV is related to virulence-related genes that regulate the NF-κB signaling pathway (Silk et al. 2007), host innate immune responses (including interferon (IFN) production, the IFN-JAK-STAT signaling pathway, and inflammatory responses) (Correia et al. 2013; Razzuoli et al. 2020), cell death (apoptosis, necrosis, and pyroptosis) (Dixon et al. 2017; Galindo et al. 2008), and autophagy (Banjara et al. 2019; Hernaez et al. 2013). In this review, we summarize the research advances on ASFV immune evasion mechanisms in African swine fever patients (Table 1). As a result, it is critical to screen for and discover virulence-related ASFV genes, as well as to understand their pathogenic pathways in ASFV-infected pigs, as this will provide vital insights into developing safer and more effective vaccines for preventing and managing ASF illnesses.

The first ASF case in China was reported in August 2018. Zhao identified an ASFV strain from diseased pigs in Heilongjiang Province, China, and named it ASFV Pig/HLJ/18. ASFV Pig/HLJ/18 belongs to genotype II, and its genome sequence is similar to that of ASFV Poland 2017. Pig/HLJ/18 is highly virulent in pigs, is efficiently transmissible, and causes acute disease characterized by fever and hemorrhagic signs (Zhao et al. 2019). We evaluated the transcriptome and proteome of PAMs infected with ASFV Pig/HLJ/18 and discovered that 187 viral proteins were expressed in ASFV HLJ/18-infected PAMs (data not shown).

Zhao investigated the genomes of 22 ASFV strains obtained in seven regions of China in 2020 (Sun et al. 2021a). Compared with Pig/HLJ/18, all 22 isolated ASFV strains were characterized as genotype II, which contains mutations, including deletions, insertions, or short-fragment replacements. Half of these strains harbor a mutation or deletion in the EP402R gene (encoding CD2v), leading to the loss of hemadsorption. Virulence testing in pigs revealed not only highly virulent isolates but also less virulent natural mutants with high transmissibility (Sun et al. 2021a).

Recently, genotype I ASFV strains have emerged in China (Vallee et al. 2001). Two nonhemadsorption genotype-I ASFV strains, HeN/ZZ-P1/21 and SD/DY-I/21, were isolated from pig farms in Henan and Shandong provinces, respectively. Unfortunately, researchers found three recombinant ASFV strains of genotypes I and II in Chinese pigs in 2023. These recombinant strains belong to genotype I based on the *B646L* gene, even though they contain 10 distinct fragments from the genotype II virus (Gomez-Villamandos et al. 1995). Among them, one of the recombinant viruses has high lethality and transmission in pigs. Deletion of the virulence-related genes *MGF505/360* and *EP402R* reduced its virulence. Notably, the live attenuated vaccine ASFV-7GD, derived from the genotype II ASFV Pig/HLJ/18 strain, could not protect against challenge with the recombinant virus. These findings indicate that the use of recombinant ASFV strains of genotypes I and II represents considerable hurdles to the early detection, prevention, and control of ASF in China.

ASFV infection evades host antiviral immune responses

Genome-wide transcriptomic analysis of highly virulent ASFV infection revealed that ASFV infection has significant effects on various biological processes, such as innate immunity, the inflammatory response, apoptosis, and autophagy (Cackett et al. 2020; Ramiro-Ibanez et al. 1996; Quarleri et al. 2021; Hernaez et al. 2004), suggesting that ASFV infection may evade host antiviral immune responses by targeting these pathways.

Table 1 ASFV immunomodulator gene-encoded proteins participate in viral immune evasion

Inhibition of Immunomodulation	Function	Protein name	Targeting molecule	Signaling pathway	Reference
Apoptosis	Pro-apoptosis	pE183L/p54	caspases 3	Activating effector caspase-3 apoptosis	Hernaez et al. 2004
		pE199L	BCL-X_L	Inducing the mitochondrial-dependent apoptosis	Li et al. 2021
		pEP402R/CD2v	CD58	Inducing apoptosis in swine lymphocytes/macrophages	Chaulagain et al. 2021; Huang et al. 2023a
	Anti-apoptosis	pA179L	BH3 only protein	Inhibiting apoptosis	Dixon et al. 2017; Galindo et al. 2008; Brun et al. 1996
		pA224L	Proteolytic fragment of caspase-3	Inhibiting apoptosis	Nogal et al. 2001; Neilan et al. 1997a
		pEP153R	p53	Reducing the transactivating activity of the cellular protein p53 in Vero cell cultures	Dixon et al. 2017
		pEP402R/CD2v	CSF2RA	Activating the JAK2-STAT3 pathway and inhibiting apoptosis in PAMs	Gao et al. 2023
	Induction of apoptosis by ER stress	pDP71L	Protein phosphatase 1 catalytic subunit	Recruiting the protein phosphatase 1 catalytic subunit to dephosphorylate eIF2α and inhibiting CHOP induction	Galindo et al. 2012
Innate immune responses	Inhibition of type I IFN signaling pathway	pMGF360-15R/pA276R	-	Inhibiting the upregulated expression of type I IFN stimulated by poly (I:C)	Golding et al. 2016
		pMGF505-7R/pA528R	STING, IRF3, IRF7, TBK1	Promoting the expression of the autophagy-related protein ULK1 to degrade STING; interacting with and inhibiting the nuclear translocation of IRF3; interacting with IRF7 and TBK1 to degrade IRF7 by autophagy, cysteine, and proteasome pathways and TBK1 by the proteasome pathway	Li et al. 2021; Li et al. 2021; Golding et al. 2016; Yang et al. 2022
		pMGF360-12 L	KPNA2, KPNA3, KPNA4	Inhibiting type I IFN, NF-κB, and JAK/STAT signaling by blocking the interaction of importin α and NF-κB signaling pathway	Zhuo et al. 2021
		pMGF505-11R	STING	Interacting with and degrading STING by the lysosomal, ubiquitin–proteasome and autophagy pathways	Zhang et al. 2021

Table 1 (continued)

Inhibition of Immunomodulation	Function	Protein name	Targeting molecule	Signaling pathway	Reference
		pMGF360-14 L	IRF3	Promoting IRF3 degradation through ubiquitin-meditated proteolysis	Zhang et al. 2021; Wang et al. 2021
		pDP96R	IRF3	Interacting with IRF3 to impede the translocation of IRF3 to the nucleus	Wang et al. 2018; Dodantenna et al. 2024
		pE184L	STING	Interacting with STING and impairing dimerization and oligomerization of STING	Zhu et al. 2023a
		pH 240R	STING	Interacting with STING and inhibiting its oligomerization and translocation from the endoplasmic reticulum to the Golgi apparatus	Ye et al. 2023
		pE120R	IRF3	Interacting with IRF3 and interfering with the recruitment of IRF3 to TBK1	Alfonso et al. 2007
		pI329L	TRIF	Inhibiting TLR signaling	de Oliveira et al. 2011; Henriques et al. 2011
		pI215L	RNF138, IRF9, STAT3	Inhibiting K63-linked polyubiquitination of TANK-binding kinase 1 through pI215L-binding RNF138; mediating IFR9 degradation; mediating STAT2 degradation	Huang et al. 2021; Li et al. 2022; Riera et al. 2022
		pE301R	IRF3	Interacting with IRF3 to inhibit the nuclear translocation of IRF3 induced by cGAMP and poly(dA:dT)	Liu et al. 2022
		pS273R	IRF3	Interacting with IRF3 and disrupting the association between TBK1 and IRF3	Luo et al. 2022
		pA137R	TBK1	Interacting with TBK1 and promoting the autophagy-mediated lysosomal degradation of TBK1	Sun et al. 2021a
		pI226R	cGAS	Interacting with cGAS and promoting cGAS degradation through the autophagy–lysosome pathway	Hong et al. 2022

Table 1 (continued)

Inhibition of Immunomodulation	Function	Protein name	Targeting molecule	Signaling pathway	Reference
		pM1249L	TBK1, IRF3	Inhibiting phosphorylation of TBK1 by cGAS and STING overexpression and interacting with IRF3 to induce IRF3 degradation by lysosomal pathway	Cui et al. 2022
		pL83L	cGAS, STING	Interacting with cGAS and STING to promote autophagy-lysosomal degradation of STING by recruiting Tollip	Cheng et al. 2023
		pEP364R	2′,3′-cGAMP	Interacting with 2′,3′-cGAMP and exerting their phosphodiesterase activity to cleave 2′,3′-cGAMP	Dodantenna et al. 2022
		pC129R	2′,3′-cGAMP	Interacting with 2′,3′-cGAMP and exerting their phosphodiesterase activity to cleave 2′,3′-cGAMP	Dodantenna et al. 2022
	Inhibition of RIG-I signaling pathway	pI267L	Riplet	Interacting with Riplet and disrupting Riplet-RIG-I interaction to impair Riplet-mediated K63-polyubiquitination and activation of RIG-I	Zhang et al. 2021a
	Regulation of JAK-STAT signaling	pMGF360-9 L	STAT1/2	Interacting with STAT1 and STAT2 and degrading STAT1 and STAT2 through apoptosis and ubiquitin–proteasome pathways, respectively	Zhang et al. 2022
		pMGF-360–10 L	JAK1	Targeting JAK1 and mediating its degradation	Li et al. 2023
		pMGF505-7R/pA528R	JAK1, JAK2, IRF9	Interacting with JAK1 and JAK2 and mediating their degradation; interacting with IRF9 and inhibiting the nuclear translocation of ISGF3	Li et al. 2021; Huang et al. 2023b
		pEP402R/CD2v	CSF2RA	Interacting with CSF2RA to regulate the JAK2-STAT3 pathway	Huang et al. 2023a

Table 1 (continued)

Inhibition of Immunomodulation	Function	Protein name	Targeting molecule	Signaling pathway	Reference
		pS273R	STAT2, DCST1	Interacting with STAT2 and recruited DCST1 for K48-linked polyubiquitination of STAT2 and subsequent proteasome-dependent degradation of STAT2	Li et al. 2023
		pH 240R	IFNAR1, IFNAR2	Interacting with IFNAR1 and IFNAR2 to disrupt the interaction of IFNAR1-TYK2 and IFNAR2-JAK1	Ye et al. 2024
		pF778R	STAT1	Weakening the nuclear accumulation of activated STAT1	Chen et al. 2023
Inflammatory responses	Inhibition of NF-κB pathway	pA238L	p300	Interacting with the amino-terminal region of p300 to inhibit the acetylation and transcriptional activation of NF-κB	Neilan et al. 1997b; Granja et al. 2008
		pI215L	-	Blocking p65 nuclear translocation upon cytokine stimulation	Barrado-Gil et al. 2021; Barrado-Gil et al. 2020
		pDP96R	IKKβ	Negatively regulating NF-κB signaling by inhibiting IKKβ	Wang et al. 2018
		pF317L	IKKβ	Interacting with IKKβ and suppressing its phosphorylation	Yang et al. 2021
		pI10L	NF-κB	Interacting with IKKβ to block the association of IKKβ with IκBα and p65	Chen et al. 2023
		pMGF300-2R	IKKα, IKKβ	Interacting with and degrading IKKα and IKKβ via the selective autophagy pathway	Wang et al. 2023
		pMGF360-12 L	KPNA2, KPNA3, KPNA4	Competitively inhibiting the interaction between NF-κB and nuclear transport proteins	Zhuo et al. 2021; Chen et al. 2023
		pMGF505-7R/pA528R	IKKα	Interacting with IKKα to inhibit NF-κB activation	Li et al. 2021
		pH 240R	NEMO	Interacting with NEMO and promoting the autophagy-mediated lysosomal degradation of NEMO	Huang et al. 2023b; Zhou et al. 2022
	Inhibition of NLRP3 inflammasome activation	pS273R	GSDMD	Inhibiting pyroptosis by noncanonically cleaving GSDMD	Zhao et al. 2022
		pMGF505-7R/pA528R	NLRP3	Binding to NLRP3 to inhibit inflammasome formation	Li et al. 2021

Table 1 (continued)

Inhibition of Immunomodulation	Function	Protein name	Targeting molecule	Signaling pathway	Reference
		pH 240R	NLRP3	Interacted with NLRP3 to inhibit its oligomerization	Huang et al. 2023c
Autophagy	Regulation of autophagy	pA179L	Beclin	Engaging Beclin using the same canonical ligand-binding groove that is utilized to bind to pro-apoptotic Bcl-2 proteins	Banjara et al. 2019; Hernaez et al. 2013
		pE199L	PYCR2	Interacting and downregulating the expression of PYCR2, resulting in autophagy activation	Chen et al. 2021
		p17	TOM70	Promoting mitophagy by facilitating the interaction of SQSTM1 with TOMM70	Hu et al. 2023

ASFV infection regulates cell death

Apoptosis is also known as programmed cell death (PCD). ASFV-infected tissues exhibit significant damage, accompanied by a substantial number of apoptotic cells (Li et al. 2021c; Brun et al. 1996; Nogal et al. 2001). In ASFV-infected pigs, ASFV can replicate in fibroblasts, smooth muscle cells, and endothelial cells in interstitial tissues (Brun et al. 1996). ASFV promotes viral replication and the spread of progeny viruses by regulating apoptosis (Neilan et al. 1997a). Some ASFV proteins have been confirmed to participate in regulating apoptosis (Fig. 1). For example, p54 (Chaulagain et al. 2021) and pE199L (Huang et al. 2023b) can induce apoptosis, whereas pA179L (Galindo et al. 2008; Gao et al. 2023) and pA224L (Revilla et al. 1997; Rodriguez et al. 2002) have significant inhibitory effects on apoptosis (Dixon et al. 2017).

Recently, the CD2v protein was found to induce apoptosis in swine PBMCs and macrophages (Hurtado et al. 2004). Consistent with these results, Wuang reported that the virulence and pathogenicity of mutant ASFV strains are reduced in pigs when ASFV-ΔEP402R-infected pigs are used as a model (Wang et al. 2014). However, CD2v was identified as an apoptosis inhibitor that functions by interacting with CSF2RA to regulate the JAK2-STAT3 pathway (Zhou et al. 2018). The causes for the discrepancies between these data are unknown and will require additional examination.

ASFV-encoded proteins induce apoptosis

The ASFV *E183L* gene encodes the membrane protein ASFV p54, which is largely involved in viral invasion, adhesion, and virion assembly (Galindo et al. 2012). Overexpression of p54 promotes apoptosis. The sequence of the 13-amino acid domain within p54 is similar to that of the BH3 domain of the pro-apoptotic protein Bim. ASFV p54 loses its ability to induce apoptosis without this domain (Chaulagain et al. 2021). ASFV pE199L, which localizes to the inner viral envelope, also plays a role in membrane fusion and core penetration (Matamoros et al. 2020). Recently, Li discovered that the overexpression of pE199L promotes mitochondria-mediated cell death by reducing the mitochondrial membrane potential, leading to cytochrome C release and the activation of apoptosis-related caspase-9 and caspase-3/7 (Huang et al. 2023b).

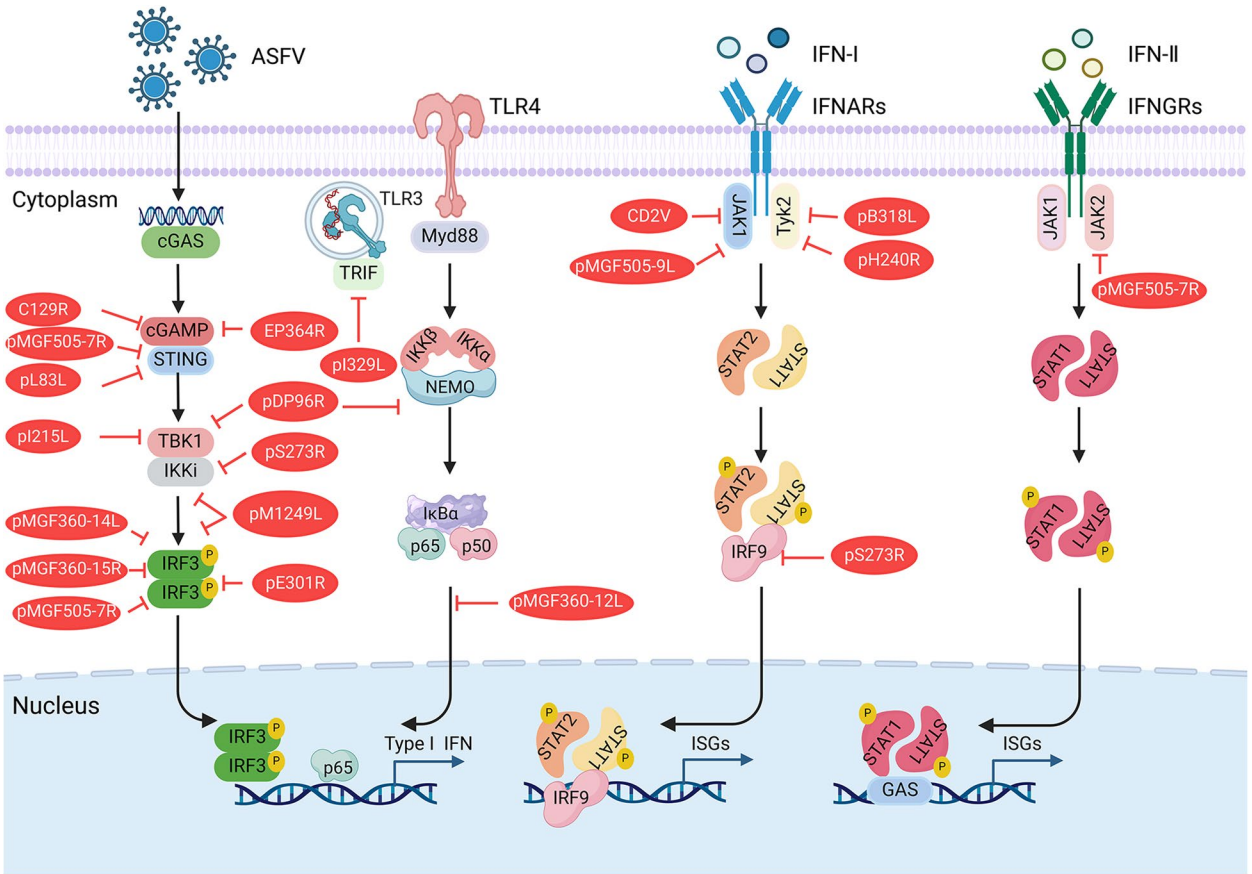

Fig. 1 ASFV-encoded proteins regulate apoptosis

ASFV-encoded proteins inhibit apoptosis

The ASFV *A179L* gene encodes a viral homolog of human Bcl-2, which contains four conserved domains (BH1, BH2, BH3 and BH4) (Dixon et al. 2017). pA179L is highly conserved and is expressed early and late during ASFV infection. pA179L mainly localizes to the mitochondria or endoplasmic reticulum (ER). Moreover, pA179L has antiapoptotic effects. Overexpression of pA179L can inhibit various types of stimulus-induced apoptosis (Portugal et al. 2018). To suppress apoptosis, pA179L forms heterodimers with pro-apoptotic proteins from the Bcl-2 family, including Bid, Bad, Bmf, Bik and Bim (Galindo et al. 2008).

ASFV pA224L belongs to the family of inhibitors of apoptosis proteins (IAPs) (Rodriguez et al. 2002). Previous studies have shown that pA224L inhibits TNF-α-induced caspase-3 activation and apoptosis (Revilla et al. 1997). Overexpression of pA224L activates the NF-κB signaling pathway, thereby inhibiting apoptosis and promoting viral proliferation by activating the transcription of a large number of antiapoptotic genes, including IAPs and Bcl-2 family members (Golding et al. 2016). Infection with the ASFV strain with a deletion of the *A224L* gene (ASFV-ΔA224L) activates caspase-3 in Vero cells. However, ASFV-ΔA224L replication in macrophages and pathogenicity in pigs do not decrease (Revilla et al. 1997).

ASFV pEP153R is similar to the N-terminal domains of certain C-type lectin molecules. PEP153R is a multifunctional protein that inhibits the expression of MHC-I molecules and prevents staurosporine-induced apoptosis or viral infection by blocking p53 protein activation (Fraczyk et al. 2016). Infection with the ASFV BA71V strain lacking the *EP153R* gene (ASFV-ΔEP153R) activates caspase-3, thereby inducing cell death. Interestingly, ASFV-ΔEP153R-infected cells lose the ability to adsorb red blood cells, suggesting that pEP153R also participates in the red blood cell adsorption process (Dixon et al. 2017).

ASFV pDP71L and pE66L inhibit ER stress-induced apoptosis

The accumulation of unfolded proteins in the endoplasmic reticulum (ER) leads to ER stress (ERS) responses in ASFV-infected cells. Persistent ERS activates the translation initiation factor 2α (eIF2α)-ATF4-CHOP signaling pathway, which triggers ERS-induced apoptosis (Fan et al. 2020; Afonso et al. 2004). ASFV pDP71L can recruit protein phosphatase 1 (PP1) to dephosphorylate eIF2α, limiting the activation of the eIF2α-ATF4-CHOP signaling cascade and increasing apoptosis and viral growth (Ayanwale et al. 2022). ASFV infection also induces the activation of caspase-12 and the upregulation of calnexin and calreticulin. ASFV infection activates transcription factor 6 (ATF6) through unfolded protein reactions (UPRs), and ATF6 prevents early apoptosis to promote viral replication (Zsak et al. 2001). ASFV pE66L was recently shown to decrease host protein translation, which is associated with the PKR/eIF2a signaling pathway (O'Donnell et al. 2015).

ASFV infection regulates host innate immune responses

Compared to ASFV infection, herpes simplex virus 1 (HSV-1) infection causes greater type I IFN production. Additionally, ASFV infection inhibits poly (I:C)-induced type I IFN production (Li et al. 2021b) and inhibits IFN-induced phosphorylation of STAT1 and STAT2 (Zhuo et al. 2021). These data suggest that ASFV-encoded proteins not only inhibit type I IFN production (Razzuoli et al. 2020) but also suppress the activation of the IFN-JAK-STAT signaling pathway, thereby inhibiting the expression of IFN-stimulated genes (ISGs), resulting in the prevention of host antiviral effects (Zhang et al. 2021a; Wang et al. 2021). Previous studies have shown that porcine type I and II IFNs inhibit ASFV replication (Wang et al. 2018), while MGF360 and MGF505 inhibit type I IFN production and enhance host antiviral responses (Zhu et al. 2023a).

ASFV-encoded proteins participate in regulating type I IFN production

ASFV infects targeted cells and releases its genetic DNA. Subsequently, the DNA sensor cGAS recognizes viral DNA to synthesize cGAMP, which then triggers the translocation of stimulator of interferon genes (STING) from the ER to the Golgi apparatus. Upon activation, TBK1 phosphorylates IRF3, and the phosphorylated IRF3 then translocated to the nucleus to induce the production of type I IFNs (He et al. 2022; O'Donnell et al. 2017).

The ASFV pMGF360 and pMGF505 members not only determine the host range of virus infection (Abrams et al. 2013) but also inhibit the production of type I IFN (Zhu et al. 2023a; Ramirez-Medina et al. 2023). Some members of the MGF360 and MGF505 families are associated with the virulence of ASFV. For example, pMGF360-15R/pA276R inhibits the upregulated expression of type I IFN stimulated by poly (I:C) but has no inhibitory effect on the JAK-STAT pathway or NF-κB signaling pathway induced by type I and II IFNs (Zhang et al. 2021a). pMGF505-7R/pA528R reduces type I IFN production by suppressing IRF3 and NF-κB transcription factors (Zhang et al. 2021a).

Recent research has suggested that certain MGF members can decrease IFN production by targeting critical molecules in the cGAS-STING signaling pathway. For example, pMGF505-7R was found to promote the

expression of the autophagy-related protein ULK1, which leads to STING degradation. In addition, pMGF505-7R also inhibits type I IFN production by interacting with IRF3 to inhibit its nuclear translocation (Li et al. 2021b). pMGF360-12 L disrupts the nuclear translocation of NF-κB by blocking the interaction between importin α and NF-κB (Andres et al. 2001), while pMGF505-11R inhibits IFN-β, ISG15, and ISG56 transcription by inhibiting cGAS-, STING- and TBK1-induced activation of IFN and ISRE (Alfonso et al. 2007). pMGF505-11R interacts with STING and degrades it through various pathways, including lysosomes, ubiquitination proteasomes, and autophagy, such as lysosomes, ubiquitination proteasomes, and autophagy (Alfonso et al. 2007). Furthermore, pMGF505-11R and pMGF360-14 L inhibit type I IFN signaling by targeting IRF3, which is activated by cGAS/STING (Alfonso et al. 2007; Sun et al. 2022a).

In addition to MGF members, additional ASFV-encoded proteins also limit type I IFN production. Previous studies have shown that pDP96R (Hong et al. 2022), pE184L (Li et al. 2023), and pH 240 L (Ye et al. 2023) inhibit the cGAS-STING-TBK1 axis, thereby negatively regulating the production of type I IFN. Consistent with these results, the three ASFV-encoded proteins pDP96R (Cui et al. 2022; Cheng et al. 2023), pE184L (Li et al. 2023), and pH 240R (Dodantenna et al. 2022) are virulence-related factors. ASFV pE120R is a structural protein involved in transporting ASFV particles from the assembly site to the plasma membrane and in the transmission of ASFV (Netherton et al. 2009). A recent study revealed that pE120R suppresses the TBK1-IRF3 interaction by binding to IRF3, resulting in decreased IRF3 phosphorylation and IFNβ production (Munoz-Moreno et al. 2016).

ASFV pI329L is a homolog of a protein from the Toll-like receptor (TLR) family that is heavily glycosylated and expressed on the cell membrane. ASFV pI329L antagonizes host innate immune responses activated by TLR3 (Riera et al. 2021) by inhibiting Toll/IL-1 receptor domain-containing adaptor (TRIF)-induced IFN-β production. Overexpression of TRIF can reverse the inhibition caused by pI329L (Franzoni et al. 2020).

Unbiased screening revealed that four ASFV proteins (pI215L, pE301R, pD345R, and pS273R) strongly suppressed cGAS-STING-induced IFN production. ASFV pI215L is a ubiquitin-binding enzyme that is essential for viral infection and replication (Zhang et al. 2022). ASFV pI215L recruits RNF138 to degrade RNF128, which inhibits the K63 ubiquitination of TBK1 by RNF128 (Li et al. 2023). ASFV pE301R interacts with IRF3 and prevents IRF3 translocation mediated by cGAMP and poly(I:C), hence limiting the generation of type I IFN (Borca et al. 1994). pS273R disrupts the interaction between IKKε and STING by interacting with IKKε, thus inhibiting IFN production (Ye et al. 2024). Recently, pA137R (Granja et al. 2006), pI226R (Neilan et al. 1997b; Chen et al. 2023b), pM1249L (Wang et al. 2023a), pL83L (Chen et al. 2023), pEP364R (Zhu et al. 2023b), and pC129R (Zhu et al. 2023b) were also found to inhibit type I IFN production by targeting key molecules in the cGAS-STING-mediated signaling pathway. Additionally, host DNA-directed RNA polymerase III (Pol-III) was found to recognize AT-rich regions of the ASFV genome, leading to viral RNA sensor RIG-I-mediated innate immune responses. pI267L interacts with Riplet and disrupts the Riplet-RIG-I connection, affecting Riplet-mediated K63 polyubiquitination and RIG-I activation (Neilan et al. 1999).

ASFV-encoded proteins regulate the IFN-JAK-STAT1 signaling pathway to inhibit the expression of ISGs

The released IFN interacts with interferon receptors (IFNAR1/2) and activates the kinases JAK and TYK2. Subsequently, STAT1 is phosphorylated to form the ISGF3 complex. The ISGF3 complex enters the nucleus to induce ISGs to combat viral infections. The ISG-encoded MxA (Gladue et al. 2021) and IFITM proteins (Zhang et al. 2021b) have anti-ASFV functions. During the ASFV evaluation process, ASFV antagonizes the IFN-mediated JAK-STAT signaling pathway to inhibit the expression of ISGs (Fig. 2). For example, ASFV infection impairs the nuclear translocation of ISGF3 by leading to proteasome-dependent degradation of STAT2 and caspase-3-dependent cleavage of STAT1 (Alcami et al. 1993). Notably, compared with PAMs infected with wild-type ASFV (ASFV-WT), PAMs infected with ASFV-ΔMGF505-7R produced relatively high levels of ISGs (Li et al. 2021b). ASFV recombinant strains in which one or more genes from the *MGF360* and *MGF505* families were knocked out were more responsive to IFN than their parent viruses (Zhang et al. 2021a; Liu et al. 2023).

Several studies have shown that numerous MGF family members negatively affect the IFN-JAK-STAT signaling pathway. MGF360-9 L inhibits the expression of antiviral genes by interacting with STAT1/2 and promoting their degradation. Consistent with these results, the replication capacity of ASFV-ΔMGF360-9 L is reduced in PAMs, and its virulence in pigs is also reduced (Sun et al. 2022b). Li et al. reported that ASFV pMGF-360-10 L significantly inhibits the activation of the IFNβ promoter reporter and the production of ISGs. Compared with those in the parental ASFV CN/GS/2018 strain, more ISGs are induced to inhibit viral replication in ASFV-ΔMGF360-10 L-infected PAMs (Tran et al. 2022a). pMGF360-10 L mediates the K48-linked ubiquitination of JAK1 by recruiting HECT and RLD domain-containing

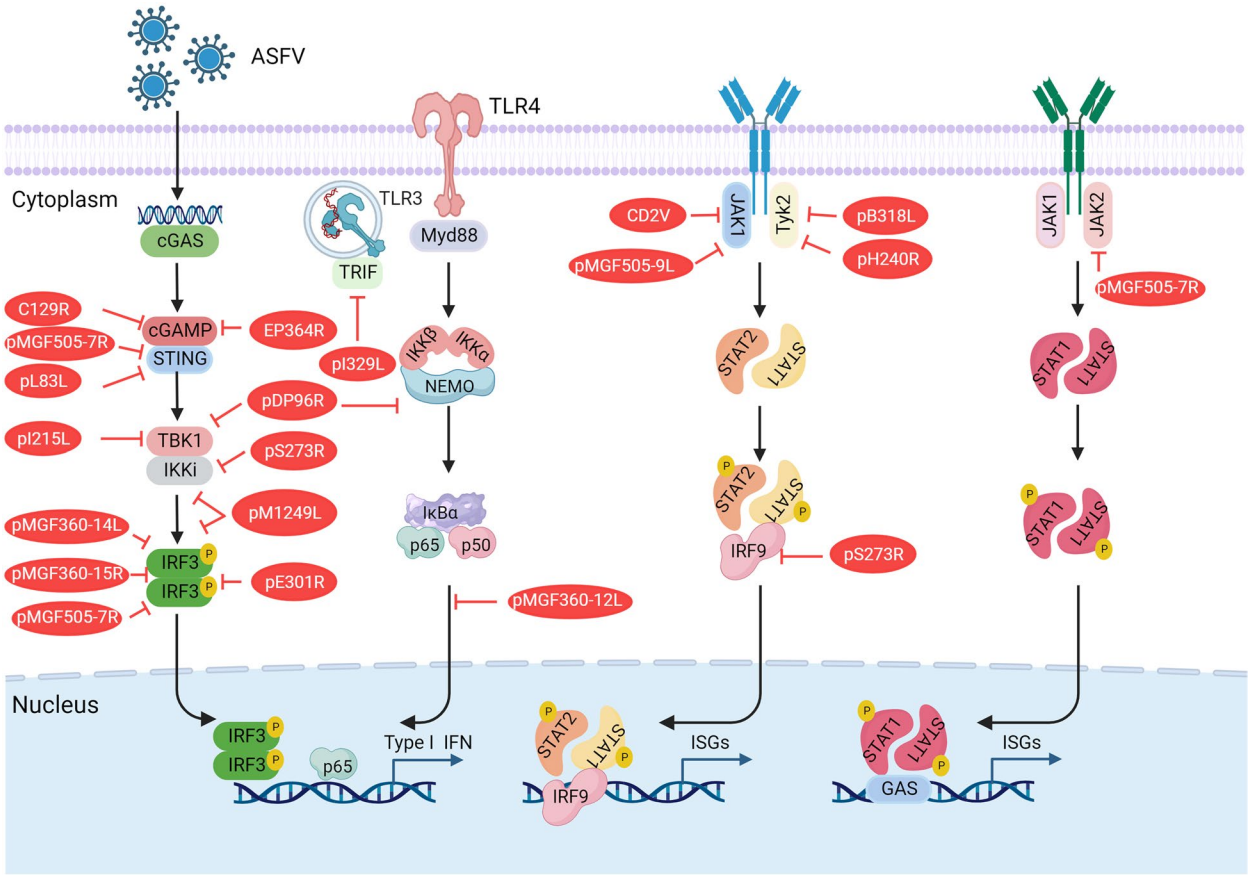

Fig. 2 ASFV-encoded proteins inhibit interferon production and the JAK-STAT signaling pathway

E3 ubiquitin protein ligase 5 (HERC5) (Tran et al. 2022a). pMGF505-7R inhibits the IFN-JAK-STAT signaling pathway activated by IFN-γ, promoting the degradation of JAK1 and JAK2 by upregulating the E3 ubiquitin ligase RNF125 and inhibiting Hse5 expression (Li et al. 2021a).

CD2 is a T lymphocyte surface adhesion receptor. ASFV *EP402R*-encoded CD2v is a type I transmembrane protein that is homologous to CD2 (Borca et al. 2023). Compared with ASFV Pig/HLJ/18 infection, ASFV-ΔCD2v infection induced higher levels of IFN and ISGs in PAMs. Mechanistically, CD2v interacts with STING and IRF3 to inhibit their nuclear translocation, thereby inhibiting type I IFN production. In addition, CD2v (Wang et al. 2014) and pH 240R (Tran et al. 2022b) also inhibit the IFN-JAK-STAT signaling pathway through their interaction with IFNAR1 and IFNAR2, thereby inhibiting host antiviral immune responses. Recently, a study reported that pS273R interacts with STAT2 and recruits the E3 ligase DCST1 to modify STAT2, thus promoting the degradation of STAT2 to inhibit IFN production and ISG expression, which is independent of pS273R enzyme activity (Chandana et al. 2024). In addition, pF778R is a crucial subunit of ASFV ribonucleotide reductase. Chen et al. reported that pF778R can impede IFN-JAK-STAT signaling by weakening the nuclear accumulation of activated STAT1 (Rivera et al. 2007).

ASFV infection regulates inflammatory responses

ASFV infection regulates the NF-κB signaling pathway

Previous studies have shown that pA238L inhibits the expression of proinflammatory cytokines by regulating the transcriptional activities of NF-κB, NF-AT, and c-Jun (Zhang et al. 2010). Consistently, *A238L*-deficient strain (ASFV-ΔA238L)-infected pigs showed increased expression of TNFα. However, the replication capacity and virulence of the ASFV-ΔA238L strain generated from the Malawi Lil-20/1 strain did not significantly change compared with those of the parental strain (Zsak et al. 1996). The different backgrounds of ASFV isolates could result in conflicting data.

Recently, pI215L, pDP96R, and pF317L were found to inhibit the activation of NF-κB. For example, pI215L inhibits the activation of NF-κB by preventing the entry of p65 into the nucleus (Afonso et al. 1998), thereby

inhibiting host protein synthesis (Qi et al. 2023). pDP96R blocks IKKβ-mediated NF-κB promoter activity (Hong et al. 2022). pF317L interacts with IKKβ and inhibits its phosphorylation, which enhances the stability of IκBα. The accumulation of IκBα prevents NF-κB activation. Knocking down pF317L expression can enhance viral replication (Reis et al. 2017). Ren reported that ectopically expressed pI10L significantly suppressed the activation of NF-κB signaling. Mechanistically, ASFV pI10L inhibits IKKβ phosphorylation by reducing the K63-linked ubiquitination of NEMO, resulting in reduced phosphorylation of IκBα and p65. In agreement with these results, recombinant ASFV lacking the *I10L* gene (ASFV-ΔI10L) induced higher levels of proinflammatory cytokines in PAMs than did the parental ASFV HLJ/18 strain (Ran et al. 2022; Chen et al. 2020).

MGF members and pH 240R regulate NLRP3-dependent inflammatory responses

ASFV infection does not induce severe inflammatory responses or pyroptosis in PAMs. Recent studies have shown that MGF members are involved in regulating inflammatory responses (Fig. 3). For example, the *MGF300-2R* gene, which promotes IKKα and IKKβ degradation through the autophagy pathway, is critical for viral replication in PAMs (Rathakrishnan et al. 2021). Consistently, the viral titer of recombinant ASFV lacking the *MGF300-2R* gene (ASFV-ΔMGF300-2R) decreased by 1 log. Additionally, it induced greater interleukin (IL)-1β and TNFα production in PAMs than did ASFV-WT. Importantly, both the replication and virulence of ASFV-ΔMGF300-2R were significantly lower than those of ASFV-WT in pigs (Rathakrishnan et al. 2021). pMGF360-12 L could block NF-κB activation induced by cGAS-STING, TBK1, and IKKβ (Ran et al. 2022). In addition, pMGF360-12 L interacts with KPNA2, KPNA3, and KPNA4, inhibiting the interaction of p65 with these three proteins, which consequently inhibits the nuclear translocation of NF-κB (Andres et al. 2001).

ASFV pMGF505-7R and pH 240R interact with NLRP3 to inhibit ASC oligomerization, thereby inhibiting caspase-1 activation and IL-1β secretion (Huang et al. 2023a; Li et al. 2021b). Additionally, pMGF505-7R interacts with IKKα in the IKK complex to inhibit the activation of

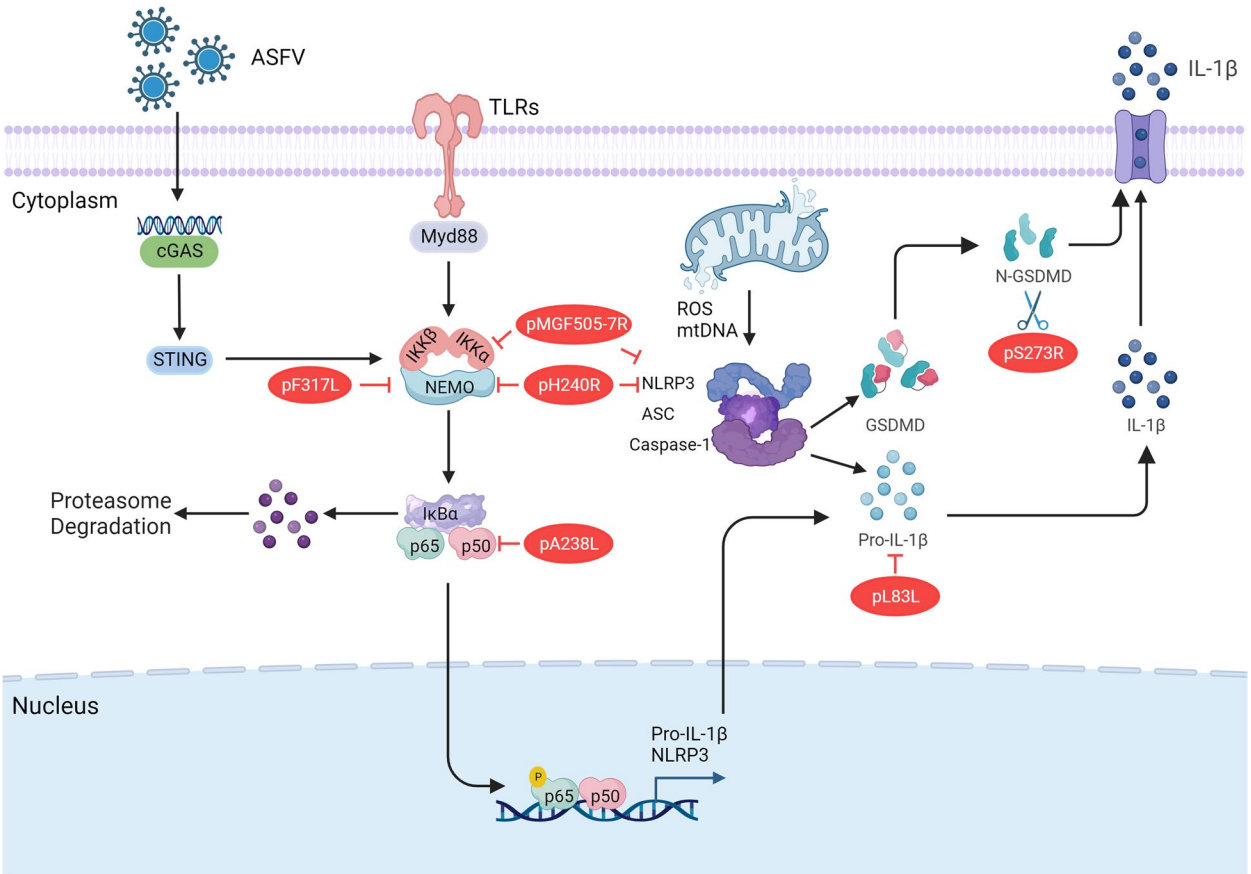

Fig. 3 ASFV infection regulates inflammatory responses

NF-κB. Compared with those of the parental strains, the levels of inflammatory cytokines and type I IFN production in PAMs infected with ASFV-ΔMGF505-7R were greater. Animal experiments have shown that the replication level and pathogenicity of ASFV-ΔMGF505-7R are reduced compared to those of its parental virus (Li et al. 2021b). Huang et al. reported that pH 240R interacts with NEMO and disrupts the IKK complex, resulting in the inhibition of NF-κB activation. pH 240R also interacts with NLRP3, which inhibits the formation of the NLRP3 inflammasome, thereby reducing the production of IL-1β (Huang et al. 2023a).

During ASFV infection, activated caspase-1 specifically cleaves Gasdermin D (GSDMD), generating an amino-terminal fragment of GSDMD (GSDMD-$N_{1\text{-}279}$) (Neilan et al. 2002). Furthermore, ASFV pS273R cleaves GSDMD-$N_{1\text{-}279}$ to produce GSDMD-$N_{1\text{-}107}$ and GSDMD-$N_{108\text{-}279}$ fragments, neither of which triggers pyroptosis. These data suggest that ASFV pS273R negatively regulates host antiviral inflammatory responses by cleaving GSDMD to enhance virus replication (Neilan et al. 2002).

ASFV infection regulates autophagy

Previous research has indicated that ASFV infection is linked to autophagy. Some ASFV-encoded proteins may induce autophagy through various pathways. For example, pA179L interacts with Beclin through its BH3 homology domain to inhibit autophagy, which may play a role in blocking autophagy during ASFV infection (Banjara et al. 2019; Hernaez et al. 2013). ASFV pE199L induces complete autophagy by interacting with the autophagy-associated protein PYCR2 and downregulating its expression (Reis et al. 2016). ASFV p17 promotes mitophagy by enhancing the interaction between SQSTM1 and TOM70 (Borca et al. 1998).

Strikingly, several ASFV-encoded proteins were found to participate in regulating innate immune responses by promoting autophagy-mediated degradation of key molecules in the cGAS-STING signaling pathway. ASFV pMGF505-7R inhibits type I IFN production by degrading STING through autophagy (Li et al. 2021a). Recently, pMGF110-9 L (Monteagudo et al. 2017) and pA137R (Granja et al. 2006) were found to promote autophagy-mediated degradation of TBK1, resulting in the inhibition of type I IFN production. ASFV pL83L interacts with cGAS and STING, promoting autolysosomal-mediated degradation of STING through Tollip recruitment, thereby reducing the production of IFN-I (Chen et al. 2023).

Prospective

ASFV is challenging to control for a variety of reasons, the primary one being our lack of understanding of its epidemic features, infection, and immune evasion. Additionally, the pathogenesis and immune protection mechanisms of ASFV are not well understood.

In the past 30 years, scientists have confirmed that some ASFV genes that regulate host antiviral innate immune responses are related to the virulence of ASFV strains. Knocking out these genes does not affect the replication ability of ASFV strains, but it reduces the virulence of ASFV (Zhang et al. 2021a; Ramirez-Medina et al. 2023; Rathakrishnan et al. 2022; Hu et al. 2023). Immunizing pigs with these live attenuated vaccine-candidate strains can provide partial or complete protection (Monteagudo et al. 2017; Luo et al. 2022). However, their safety, stability, and ability to generate cross-protection require further investigation. It is worth noting that pigs immunized with a live attenuated vaccine are more difficult to detect than those immunized with ASFV-WT. Therefore, the virus can suddenly spread throughout the herd, which has important effects on the reproductive performance of sows. However, until recently, most scientists in the ASFV field believed that live attenuated vaccines are the most promising. Identifying and describing the essential virulence-related genes will provide a theoretical foundation for the safe and effective production of live attenuated vaccines.

Accumulating evidence shows that the pathogenicity of ASFV isolates is closely related to ASFV immunomodulatory genes, the genetic background of these ASFV isolates, and the feeding status of the animals. Some viral genes determine virulence in a particular strain, but knocking out these genes in another strain may alter but not change the virulence of ASFV. Therefore, the identification and confirmation of a key immunomodulatory virulence gene should be considered in the context of ASFV strains and other contributing factors.

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Authors' contributions

C.W. wrote the original draft, reviewed and edited it.

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Availability of data and materials

All relevant data are within the article.

Declarations

Competing interests

The author declares that he has no conflicts of interest with others. Author Changjiang Weng was not involved in the journal's review or decisions related to this manuscript.

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