African Swine Fever Virus; Invasion and Modulation of Host Defenses Responses

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Abstract

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Running Head: ASFV; modulation of host defences responses

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Abstract

The tremendous global surging of the African Swine Fever Virus (ASFV) threatens pig industries worldwide. ASFV causes acute hemorrhagic fever in domestic pigs with near enough 100 % mortality, whereas immune in its natural host's warthogs, bush-pigs, and the soft tick vector. ASFV is a large cytoplasmic double-stranded DNA virus that replicates mainly in macrophages. At present, infected animals can only be managed by quarantine and removal of infected animals as lack of effective vaccines and treatment. This review focus on mechanisms by which ASFV enter, replicate, modulate, molecular hijacking and overpowered the host immune system. Various machinery employed by ASFV discussed, such as overcoming barriers to replication in the monocyte/macrophage, inhibition of apoptosis, inhibition of inflammatory responses, ASFV adhesion protein CD2v. This review exposes ASFV evasion strategies and virus-host interactions, thus reveal promising vaccine development ideas.

Introduction to African Swine Fever Virus (ASFV)

African Swine Fever (ASF) is a highly contagious and deadly haemorrhage disease of swine with extensive virulence in morbidity and high mortality rates that approach 100% (Gallardo et al., 2015). Currently, vaccines and treatments are not available; the disease can only be managed by quarantine and removing infected animals. This disease is endemic in sub-Sahara Africa, Asia, and Europe, which affects the pork industry in those regions and also causes socio-economic losses worldwide (Costard et al., 2009). The diseases are characterized by high fever, haemorrhages, ataxia, bleeding, and depression in swine.

A large double-stranded DNA virus causes ASF with a complex molecular structure. African Swine Fever Virus (ASFV) is a cytoplasmic replicated virus that belongs to the superfamily of nucleocytoplasmic large DNA viruses (NCLDV) (Dixon et al., 2005, 2008; Iyer et al., 2006; Yutin et al., 2009). African Swine Fever Virus belongs to a member of the Asfarviridae family, genus Asfivirus (Dixon et al., 2008). In Africa, Ornithodoros species like warthogs, bushpigs, and soft ticks are the virus long-term reservoir hosts without significant clinical signs. ASFV has icosahedral morphology with an average diameter of 200nm. The genome consists of nucleoids wrapped by a protein core-shell, an inner lipid membrane, protein capsid, and other membranes. ASFV genome contains double-stranded DNA of 170-194kbp single linear molecule, covalently close-ended.

Understanding the mechanisms ASFV uses to invade and modulates host defense responses to infection will buttress strategies and knowledge accurately needed for vaccine development.

ASFV DNA genome encodes many proteins; about 160 non-essential of the said proteins have no value for virus replication but play essential roles in evading and modulating host defences response. ASFV codes for many proteins which inhibit interferon responses, antiviral response. The virus target replication cells are the mononuclear phagocyte system having critical roles in activating innate and adaptive responses. Therefore, ASFV rendering these cells incapacitated by profoundly manipulating their functions in response to infections (Dixon et al., 2019).

An essential feature of host defence, operating immediately upon infection with these viruses, is a cell's capacity to induce intrinsic and innate immune responses against DNA viruses. These host defences function to prevent viral infection as well as to support the adaptive immune responses within the host organism and to promote a global antiviral environment. As such, for the survival of the host and the preservation of a balanced system, these immune processes' role is essential. Immune system misregulation is associated with the progression of debilitating autoimmune disorders, including type I diabetes, multiple sclerosis, and erythematosus lupus (reviewed in Lang et al., 2007).

In this review, mechanisms by which ASFV invade and manipulate host defences system were described, such as overcoming barriers to replication in the monocyte/macrophage, inhibition of apoptosis, inhibition of inflammatory responses, ASFV adhesion protein CD2v.

2. ASFV Entry Mechanisms

Adsorption and entrance of the viral particles into the host cell initiate the infection cycle of ASFV. Previous researches on ASFV indicated that the entry and adsorption are mediated by low pH and temperature-dependent process with consistent saturable and specific receptor-mediated endocytosis in Vero cells and porcine macrophages (Valdeira and Geraldes 1985; Alcami et al., 1989). Though the receptor(s) for the virus remains unclear, it's a fact that infection of ASFV results from the macrophage-specific receptor.

The virus spreads into cells by either receptor-mediated endocytosis clathrin-coated pits or a less precise process, macropinocytosis (Hernaez and Alonso, 2010; Hernaez et al., 2016; Sanchez et al., 2012). It was earlier suggested that the primary mechanism of virus entry into the cell is through receptor-mediated endocytosis, but the binding and entry cellular receptor(s) are unknown.

Sanchez-Torres et al. (2003) reported that the receptor for ASFV might be CD163. However, Popescu et al. (2017) research revealed that deletion of the CD163 gene from the pig genome did not limit ASFV replication in cultured macrophages and did not reduce virulence in pigs. The dynamic, multilayered structure of ASF

Virion brings more complexities to these problems. Both the mature intracellular and enveloped extracellular forms of the virus are contagious. When the virus particles migrate to the acidic environment of late endosomes, its outer shell, which is acquired when the virus buds across the plasma membrane, is destroyed (Hernaez et al., 2016). The inner virus envelope fuses with the endosomal membrane that releases the virus core particle into the cytoplasm (Hernaez et al., 2016). Several viral proteins, including p54/pE183 L, p30/pCP204 L, and p12/pO61R, have been identified as necessary in the binding and entry mechanism, but the cellular receptors are not known (Alcami et al., 1992; Gomez-Puertas et al., 1998; GomezPuertas et al., 1996). ASFV infection enters into the endocytic pathway by any of the paths described above (Cuesta-Geijo et al., 2012).

The virus must pass through a diverse endosome population to accomplish a fruitful infection (Fig. 1). Proteins and lipids recruited to the endosomal membrane orchestrate the maturation of the endocytic pathway. The Rab GTPase protein family is a significant regulator of the endosomal maturation pathway, with each Rab member belonging to a distinct endosomal compartment (Stenmark 2009). Between 30-45 min post-infection (mpi), viral decapsidation occurs in mature endosomal compartments due to the acidic intraluminal pH. When virus particles are decapsidated, the inner envelope is exposed, allowing interaction and subsequent fusion of the viral membrane with the restrictive membrane of endosomes, allowing naked cores to be released into the cytosol and replication to begin (Cuesta-Geijo et al., 2009).

Replication in macrophages and monocytes

Early researches reported that replication of ASFV DNA occurs at perinuclear cytoplasmic viral assembly sites. Virus entry into the cytoplasm from partially uncoated core particles triggered the enzyme's DNA replication expression. Initial transcription employs transcription and transcript processing enzymes encoded by viruses packaged in the core (Kuznar et al., 1980b; Salas et al., 1983).

ASFV primarily replicates in macrophages because of its vital role in the host's innate and adaptive responses being activated and coordinated; this gives the ASFV virus the essential advantage of stopping or regulating these responses. However, as macrophages are at the forefront in identifying and eliminating pathogens and activation of the host's protection, this tactic comes at a cost. Macrophages and Monocytes are the critical cells infected by this virus in vitro and in vivo study in pigs (McCullough et al., 1999).

Responses of macrophages to ASFV

Macrophages and Monocytes play a crucial role in the induction of innate immune responses, responding to specific pathogen-associated signals. These cells also present antigen to T cells to activate the adaptive immune response, which is vital for developing a protective immune response (Correia et al., 2013; Haig, 2001; Janeway and Medzhitov, 2002).

Macrophages are expert in recognition and destruction of pathogens and initiation of an inflammatory response.

In response to intercellular signals, macrophages have exceptional plasticity and can follow various phenotypes and functions (Mosser and Edwards, 2008). Macrophages function extraordinary in response to intercellular signals such as phagocytosis initiation, increased cell size and eventual activation of different secretory signals, including cytokines and chemokines (Kawai and Akira, 2009; Mogensen, 2009).

ASFV manipulating replication in Monocyte/Macrophage

The oxidizing condition that can cause DNA damage and the aggregation of mutations that could prevent virus replication are the difficulties virus replication encountered in the macrophage. The acquisition of a base excision DNA repair (BER) mechanism containing a DNA polymerase X, a type I DNA ligase and an AP endonuclease requires a particular adaptation of ASFV to replicate in this setting. Deletion of either DNA polymerase X or AP endonuclease encoding genes results in compromised development of the virus and an elevated incidence of DNA virus mutations in macrophages relative to Vero cells. These results support repair enzymes' role in preserving macrophage viral genetic material (Redrejo-Rodriguez and Salas 2014).

ASFV also encodes a protein, A238L, which inhibits host transcription factors involved in initiating host defence protein transcription, including synthase inducible nitric oxide (Granja et al., 2006).

BER pathway components are packaged in virus particles, ready for use when the virus core particles enter cells early during replication. For efficient replication in macrophages, but not in tissue culture cells, the virus-encoded nucleotide metabolism enzyme, i.e. thymidine kinase, is also essential. This is probably meant to increase the pools of dNTPs needed to replicate the virus genome but present in non-dividing macrophages at relatively low levels. In virulent Georgia isolate deletion of this gene attenuated the virus in pigs, most likely due to the reduced capacity of the virus to reproduce in macrophages (Table 1) (Sanford et al., 2016).

Host innate and adaptive responses to inhibition type I interferon responses.

As a cytoplasmic DNA virus, the DNA sensing pathway is likely to be the gateway to ASFV infection sensing and type I IFN induction. However, identification of double-stranded RNA, either transcribed by cytoplasmic host RNA polymerase III from viral DNA or by viral RNA polymerase, is also likely to play a role in sensing type I interferon infection and induction. The relative significance of various pathogen-associated molecular patterns (PAMPs) and pattern recognition receptors (PRRs) involved in type I IFN induction in macrophages infected with ASFV is currently unclear (Dixon et al., 2016).

ASFV encodes a series of proteins that suppress type I interferon (IFN) transcription, cytokines, chemokines, adhesion molecules, and other genes that are immunomodulatory. Secreted IFNs are detected in infected and surrounding cells by cell surface receptors, resulting in interferon-stimulated genes being expressed (ISGs). These have roles in viral replication regulation, in dendritic cell maturation, leading to the cross-presentation of viral antigens to CD8+ cells, and natural killer cell activation. Virulent ASFV isolates inhibit type I IFN and ISGs expression in macrophages infected.

Various multigene family members (MGF) and MGF530 deletion mutant virus studies demonstrate that these genes inhibit IFN induction and may also influence the STAT (signal transducer and activator of transcription proteins) signalling cascade and antiviral state components (Afonso et al., 2004; Reis et al., 2016)

Significantly, pigs are attenuated by recombinant viruses with identical MGF360 and MGF530 deletions originating from three distinct genotypes (Afonso et al., 2004; O'Donnell et al., 2015; Reis et al., 2016). This means that in viral pathogenesis, regulation of the IFN response plays a key role. However, the report from the deletion of genes from MGF360 and MGF530 families noticeably reduced viral replication in ticks (Reis et al., 2016).

The recent finding that ticks may have an IFN-like mechanism that depends on STAT signalling raises the hypothesis that these genes may have evolved in both the mammalian and the arthropod host to modulate parallel pathways.

Furthermore, in macrophages that are infected with virulent ASFV, type I IFN induction is suppressed. However, deletion of several genes belonging to the 360 (MGF360) and MGF530/505 multigene families result in enhanced type I IFN induction and type I IFN induced genes in contaminated macrophages **(Table 1)** (Afonso et al., 2004; Reis et al., 2017). These findings suggest that type I interferon development is suppressed by at least some members of these gene families. By inhibiting IRF3 through a mechanism independent of IRF7 and NF-ϰB transcription factors, MGF360-15R (A276R) inhibits the activation of type I IFN through both TLR3 and the cytosolic sensing pathways. Therefore, it generates a small cellular type I IFN response (Correia et al., 2013). By inhibiting both IRF3 and NF-ϰB transcription factors, MGF505-7R (A528R) inhibits type I IFN induction. This protein also inhibits IFN signaling Type I and II (Correia et al., 2013).

Their mechanism(s) of action remain enigmatic considering these genes' role in inhibiting the IFN response. With some redundancy in its mechanism of action, ASFV encodes many other proteins that modulate the host's innate immunity. Both I329L, a viral TLR homologue, and A528R, for instance, inhibit Poly (I:C) IFN induction upstream of IRF3 and NF-ϰB activation (Correia et al., 2013). Close to cellular TLR3, the ASFV

I329L protein is a heavily glycosylated protein expressed in the cell membrane that inhibits TLR3-mediated IFN-β induction and activation both NF-ϰB and IRF3. To target TRIF, an adaptor protein in this pathway, the pI329 L protein was indicated. TRIF overexpression reversed the inhibition of activation of NF-ϰB and IRF3 (de Oliveira et al., 2011; Henriques et al., 2011).

The gene MGF360-15R inhibits the same pathway but at the IRF3 level. Cellular reactions to type I and type II IFN, a clear example of a viral multifunctional protein, have also been shown to suppress the A528R gene. Virulent isolates are immune to IFN (Golding et al., 2016) pre-treatment of macrophages, suggesting that ASFV prevents the antiviral state as well.

As possible targets of ASFV, two host ISG proteins have arisen. There are the family members of interferon-induced transmembrane (IFITM) proteins that control viral entry/uncoating and MxA that influences viral replication (Munoz-Moreno et al., 2016; Nethwrton et al., 2009). Since several hundred ISGs are identified, other candidates are likely to contain the replication of ASFV and virus factors that resolve these barriers.

Apoptosis inhibition

A typical cellular response to viral infection is the induction of cell death by apoptosis; this affects viral progeny reproduction and dissemination. As a result, certain viruses have evolved pathways in the infected cells to prevent apoptosis. Replication of ASFV involves subversion of many host pathways resulting in rapid cell death via programmed mechanisms such as apoptosis, necrosis, and pyroptosis. The virus subverts these to hold the host cell intact long enough that the progeny can be replicated. ASFV stimulates apoptosis both in vitro and in vivo, and in the absence of viral replication, apoptosis is induced in cultured cells. After DNA replication has begun, apoptotic signatures in infected cells are detected, and the virus encodes at least four proteins that associate with the programmed cell death pathway. A179L, A224L, and EP153R can inhibit apoptosis, while E183L can activate it (Dixon et al., 2019; Dixon et al., 2018).

ASFV A179L Protein

The protein A179L belongs to the B-cell lymphoma-2 (Bcl-2) family (Brun et al., 1996; Revilla et al., 1997). With the existence of up to 4 Bcl-2 homology regions (BH1- BH4) and their interactions with other proteins from the Bcl-2 family, members of this family may be either pro-apoptotic or anti-apoptotic. BH3-only proteins constitute the apoptosis inducers, which sense cellular damage and initiate the death process (Kvansakul et al., 2017; Youle and Strasser, 2008).

BH3-only proteins include Bim, Bid, Puma, Noxa, Bmf, Bik, Bad which Hrk, and operate either by activating Bak and Bax sequestering neutralizing the members of Bcl-2 pro-survival (Dixon et al., 2019). The A179 L protein contains similar domains to all BH domains and interacts only with domain proteins of several pro-apoptotic BH3.

A179L has a high binding affinity with a spectrum of peptides coding for BH3, structurally of A179 L bound to BH3 domain peptides from Bid and Bax (Banjara et al., 2017).

The wide variety of interactions with both the upstream pro-apoptotic BH3 domain proteins and the downstream Bak and Bax proteins is likely to ensure that apoptosis is broadly blocked within infected cells and in the various hosts of the virus (Fig. 2) (Banjara et al., 2017; Galindo et al., 2008). The A179 L protein also has a possible role in inhibiting autophagy by binding to Beclin-1's BH3 domain; this has the ability for the swine leukocyte antigen 1 (SLA 1) complex to modulate peptides introduced to T cells (Fig. 2) (Hernaez et al., 2013). At present, there is a lack of data on the targets and effect of A179 L on infected cells, especially macrophages and monocytes, the primary target cells for in vivo replication.

The A179 L protein is expressed in the early and late post-infection of ASFV cells but is not packaged into the virus particles (Afonso et al., 1996; Alejo et al., 2018); this indicates that during infection, A179 L could be involved in inhibiting apoptosis, but not at the earliest stage when virus cores enter the cytoplasm.

ASFV A224L Protein

The A2224L protein is a cellular inhibitor, and it belongs to a member of the inhibitor of apoptosis (IAP) protein family of genes which stimulate protection of cells from external induction of apoptosis through interaction with caspase-3 (Nogal et al., 2001). Its expression inhibits stimulus-induced apoptosis, like TNF-α. Increased caspase 3 activity was observed in cells infected with ASFV from which the A224L gene was deleted. A224 L inhibits caspase 3 activation and is thus capable of caspase 3 activated apoptosis. The machinery by which this is mediated has not been identified but could include direct binding to caspase 3 of A224 L (Fig. 2). A224 L expression has been shown to cause NF-ϰB, possibly inhibiting apoptosis by triggering transcription of various anti-apoptotic genes, including members of the family of IAP and Bcl-2. ASFV A224L is expressed as a late protein and is packaged into viral particles that suggest probable functions directly after the cytoplasm entry of virus cores and later during infection (Nogal et al., 2001; Rodriguez et al., 2002).

Deletion of the A224 L gene from the virulent isolate genome did not decrease replication of ASFV in macrophages or domestic pig virulence (Table 1) (Neilan et al., 1997a).

ASFV DP71L protein

ASFV DP71L is an inhibitor of stress-induced apoptosis by inhibiting the global shut-off of protein synthesis. Cell infection leads to cellular stress activation, such as the induction of endoplasmic reticulum stress to activate the unfolded protein response (UPR). This results inactivation of the protein kinase PERK resident endoplasmic reticulum. Protein kinase PKR, triggered by double-stranded RNA, is often activated by virus infection. These activated protein kinases phosphorylate initiation factor of translation eIF2α. To dephosphorylate eIF2α and restore global protein synthesis, the ASFV DP71L protein recruits host protein phosphatase 1 (PP1) (Fig. 2). As a result, pro-apoptotic transcription factor CHOP activation is inhibited, thereby inhibiting apoptosis induced by this pathway (Rivera et al., 2007; Zhang et al., 2010). However, deletion of the DP71L gene from ASFV did not lead to increased phosphorylation in mammalian cells of eIF-2α, indicating that the virus has other complementary functions to decrease phosphorylation eIF2α (Zhang et al., 2010).

Protein Phosphate 1 (PP1) has several distinct cellular roles mediated by the protein's interaction with multiple regulatory subunits, and PP1 is relatively conserved as a result. By blocking PKR activation, other viruses inhibit eIF2α phosphorylation. Because of pathogen strain, this may have contributed to the comparatively high divergence of PKR to evade this crucial antiviral defence. In diverse mammalian and arthropod hosts, the targeting of preserved points of essential pathways, such as PP1 rather than PKR, can lead to the efficient replication of ASFV.

In infected cells with DP71L gene deleted from Malawi Lil20/1 or E70 isolates, it was reported that no increase in phosphorylation of eIF-2α or CHOP induction was detected, compared with cells infected with wild-type viruses. This indicates that ASFV encodes this pathway's other inhibitors (Zhang et al., 2010). DP71 L may be necessary for some isolates for virulence, but not others. Deletion of long and short type DP71 L from the Malawi Lil20/1 and Pretoriuskop/96/4 isolates, respectively, did not affect virulence in domestic pigs and pigs, resulting in a 100% event fatality rate (Table 1) (Afonso et al., 1998b). Deletion of the short form of DP71 L from the E70 isolate of ASFV, on the other hand, resulted in virus attenuation (Zsak et al., 1996). Differences in the gene complement encoded by these viruses account for the differences observed, such as the absence of E70 genes in other isolates that may compensate for the lack of DP71 L.

ASFV PE153R Protein

The ASFV is a protein-containing C-type lectin domain that has also been identified to inhibit apoptosis, operating via the p53 and caspase 3 activation pathways (Hurtado et al., 2004). It could explain its mechanism of action as p53 inhibits specific apoptosis inhibitors (Granja et al., 2004a). The EP153R gene deletion did not decrease virus virulence in pigs. Increased apoptosis after macrophage infection was caused by recombinant ASFV lacking C-type lectin EP153R (Hurtado et al., 2004); this indicates that this protein could also play a role in controlling programmed cell death.

ASFV's PA238L inhibition of inflammatory responses

Ankyrin repeats are found in the pA238 L protein, identical to those in the NF-ϰB transcription factor I-kB inhibitor. Furthermore, to its role in the activation of the IFN type I promoter, the NF-ϰB transcription factor is needed for transcriptional activation of various inflammatory responses.

Inhibition of NF-ϰB activation was the first feature identified (Powell et al., 1996). Subsequently, pA238 L was shown to bind to and inhibit calcium/calmodulin-regulated phosphatase calcineurin (CaN), thus inhibiting the active pathways of this phosphatase, including the cytoplasmic T cell activated nuclear factor (NFAT) family of transcription factors (Miskin et al., 2000, 1998). NFAT factors are present in resting cells as hyper-phosphorylated forms in the cytoplasm and translocate to the nucleus when dephosphorylated by calcineurin to activate transcription NFAT-dependent genes. Further complexity was introduced because it was shown that A238 L inhibits transcriptional activation mediated by multiple factors that interfere with the transcriptional co-activator p300/N-terminal CBP's domain. NF-ATc2, NF-ϰB, and c-Jun contained these (Granja et al., 2008, 2009). PA238 L has been shown to shuttle between the cytoplasm and the cell nucleus following these predicted functions and is expressed as an early protein during infection (Silk et al., 2007).

Data has also accumulated that the PA238 L protein is a potent anti-inflammatory protein and has acted to suppress TNF-α induction and TNF-α stimulated pathways, inducible nitric oxide synthase, and cyclo-oxygenase synthase, both from the study of cells expressing PA238 L and deletion mutants without the gene (Granja et al., 2006, 2004b; Granja et al., 2008). The elimination of the A238 L gene from the virulent isolate of ASFV did not reduce Virus replication in macrophages or pig virulence, while TNF-α levels have increased (Salguero et al., 2008).

ASFV P183L

P183L is a putative IL-1β binding protein. At the left end of the gene, the P183L 83 amino acid protein is encoded. Using a yeast 2 (two) hybrid assay, this protein was shown to bind to IL-1β (Borca et al., 2018). The authors proposed that P183L protein may play a role in modulating this proinflammatory cytokine activity, though there is a lack of evidence for this role in vivo. This gene deletion did not decrease virus replication in macrophages or reduce domestic pigs' virulence (Table 1) (Dixon et al., 2019). This protein's functional position needs further study.

ASFV adhesion protein CD2v EP402R

An ORF, EP402R, which encodes a type I transmembrane protein, is present in the ASFV genome. The viral pEP402R/CD2v protein is identical to mammalian-encoded CD2 in its extracellular domain and comprises two Ig-like domains (Rodriguez et al., 1993). In virus transmission and immune evasion, the ASFV pCD2v/pEP402R protein has a role.

As a consequence of the association between a CD2 virus such as protein (CD2v) and its ligand expressed on these cells, infection of swine macrophages with virulent ASFV isolates induces binding of red blood cells (RBCs). The protein CD2v is also introduced into the virus particles, mediating binding to RBCs of extracellular virions (Dixon et al., 2016). Since the deletion of the CD2v gene caused a significant delay in the onset of both viremia and the development of clinical signs, this facilitates virus spread in the host. CD2v has also been shown to be immunosuppressive by inhibiting in vitro proliferation of lymphocytes (Borca et al., 1998). CD2v has also been shown to decrease viral replication in the tick vector and its role in viral pathogenesis in the mammalian host. Restoration of CD2v expression in a non-haem adsorbing isolate has potentially resulted in a significant increase in virus titers by improving virus uptake across the intestinal wall (Rowlands et al., 2009). For the maintenance of ASFV in the sylvatic cycle in which the tick vector is thought to be essential, this may be particularly important.

The only protein definitively shown to be present on the external envelope of virus particles is the pCD2v/pEP402R protein, indicating a role in virus entry or dissemination between cells (Alejo et al., 2018). The pCD2v/pEP402R cytoplasmic tail varies from that of mammalian CD2 and includes variable numbers

of a proline-rich repeat that binds to a protein-containing host SH3 domain, SH3P7/mAbp1. This protein binds to actin and has a role in transporting the vesicles (Kay- Jackson et al., 2004). The CD2v protein also associates with the AP-1 adaptor protein (Perez-Nunez et al., 2015). The data suggest a potential role for the pCD2v/pEP402R protein in vesicular transport modulation. The observed cytoplasmic tail cleavage of pCD2v/pEP402R during infection can interfere with this interaction and play a role in cellular protein localization (Goatley and Dixon, 2011).

In pigs, the role of the pCD2v/pEP402R protein in virulence depends on the virus's genetic history. Most ASFV isolates express a functional pCD2v/EP402R protein and are HAD positive. A few isolates of low virulence non-HADD have been identified (Boinas et al., 2004; Leitao et al., 2001). The deletion of the EP402R gene encoding pCD2v/pEP402R did not decrease the lethality of the virus in one sample, but there was a pause in the initiation of clinical signs and spread of the virus (Borca et al., 1998). Recent research found that deletion of the virulent isolate of the EP402R gene from the BA71 resulted in attenuation of the virus and induction of defense against virulent virus challenges (Monteagudo et al., 2017) (Table 1). One study indicated that pCD2v/EP402R is necessary for successful tick vector viral replication by increasing virus uptake across the midgut tick vector (Rowlands et al., 2009). In the propagation cycle involving warthogs, because the tick vector plays a key role, there is likely to be a selection pressure to sustain this position in that cycle.

Conclusion and research needs.

Enormous milestone researches have been achieved; in progress to understand the various mechanism and ASFV virus-encoded protein uses to interact, modulate and evade host immune responses to infection which are prerequisites strategies and knowledge needed for vaccine development. However, an effective vaccine will probably not be available in the short term but with classical control measures like early detection, biosecurity measures, culling of infected farms, epidemiology tracing, among few classical strategies to employ in the fight against ASFV.

Despite numerous researches, virus entry machinery and host cell receptors are still unknown. More research should focus on entry mechanisms and identification of ASFV host cell receptors, innate immune responses, and the virus's interaction with the host on a cellular level. Complete knowledge of this will be a possible advantage for vaccine development and exact pathogenesis. The host pattern recognition receptors involve the sense entrance of viral infection, but the IFN inhibitory proteins' mechanism is unknown.

ASFV genome contains many multigene families (MGFs), which encase many genes, e.g., MGF 360, MGF 505/530. The roles of individual genes and their mechanism of action are not clear.

The effect of the ASFV genes deleted should be studied intensively; they are also potential vaccine candidates.

Warthog are carriers of ASFV but interesting immune to it, shows no clinical symptom, further researches should be encouraged on warthog genomes, more study on its variation may expose the basis for their resistance to ASFV.

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Fig. 1. ASFV enters the host cell and progress to endosomal compartments where it got decapitated and synthesized new virions for viral factory (Galindo and Alonso 2017).

Fig. 2. ASFV modulation of host immune response through Mechanisms of apoptosis inhibition and others (Dixon et al., 2017).

Table 1

ASFV Non-essential genes (Dixon et al., 2019).

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