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Dissecting the Role of Virulence Genes in ASFV: A Molecular Perspective

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Abstract This study aims to dissect the molecular mechanisms behind ASFV virulence by focusing on its genome, key virulence factors, and interactions with host immune systems. Through an extensive review of current literature, we examine the structure and replication mechanisms of ASFV, along with the identification of critical virulence genes and their roles in immune modulation, apoptosis inhibition, and pathogenesis. Special attention is given to the A179L gene, a prominent virulence factor in ASFV, through a case study that highlights its impact on immune evasion. Additionally, the study explores the genetic variation of ASFV strains, their virulence properties, and the host's resistance mechanisms. Diagnostic tools, potential biomarkers for virulence assessment, and future directions for vaccine and antiviral development are also discussed. The findings provide essential insights into the genetic and molecular factors that contribute to ASFV virulence, with an emphasis on developing more effective diagnostic and therapeutic strategies to control ASF outbreaks. This study anticipates further advancements in ASFV research, ultimately leading to improved public health interventions and economic stability in the swine industry.

Keywords African swine fever virus; Virulence genes; Immune evasion; A179L gene; ASFV pathogenesis

1 Introduction

African swine fever virus (ASFV) is a highly contagious and lethal virus affecting domestic and wild pigs, causing significant economic losses in the swine industry worldwide. ASFV is characterized by its complex multilayered structure and large genome, which encodes numerous genes involved in immune evasion and virulence (Gallardo et al., 2018; Ju et al., 2021). The virus is known for its ability to cause nearly 100% mortality in naive pig populations, making it one of the most devastating pathogens in the swine industry. Despite extensive research, no effective commercial vaccine is currently available, complicating efforts to control outbreaks (O'Donnell et al., 2015; Li et al., 2023).

The global spread of ASFV has had a profound impact on the swine industry, particularly in regions such as Eastern Europe, Asia, and parts of Africa. The introduction of highly virulent strains, such as ASFV Georgia 2007, has led to widespread epizootics, severely affecting pig production and trade (O'Donnell et al., 2015; Vuono et al., 2022). The economic repercussions are significant, with losses not only in livestock but also in associated industries. Furthermore, ASFV poses a potential threat to food security and public health, as it disrupts the supply chain and increases the risk of zoonotic spillover, although ASFV does not currently infect humans (Gallardo et al., 2018; Reis et al., 2023).

This study attempts to dissect the role of virulence genes in ASFV from a molecular perspective, discuss the functions and contributions of specific virulence genes such as I196L, 9GL, and MGF-360-10L, and provide an overview of their potential as targets for developing live attenuated vaccines (LAVs) and other control strategies. By examining these genes, the research seeks to understand their impact on the virus's pathogenicity and explore ways to mitigate ASFV's effects on the global swine industry. Through detailed molecular analysis, the study aims to offer insights into the mechanisms of ASFV virulence and contribute to future vaccine development efforts.

2 ASFV Genome and Molecular Biology

2.1 Structure and composition of ASFV genome

The African swine fever virus (ASFV) is characterized by a large double-stranded DNA (dsDNA) genome, which encodes for more than 150 genes, many of which remain uncharacterized (Vuono et al., 2021; Ramírez-Medina et al., 2022; Ramírez-Medina et al., 2023). The genome is known to include various multigene families (MGFs) that play roles in viral replication and virulence (Wang t al., 2023). Specific genes such as A151R, E66L, and KP177R have been studied for their roles in the virus's structure and function, although not all are essential for replication in swine macrophages. The ASFV genome also contains AT-rich regions that are recognized by host immune sensors, indicating its complex interaction with host cellular mechanisms (Ran et al., 2022).

2.2 Replication mechanism of ASFV in host cells

ASFV replicates primarily in swine macrophages, where it utilizes host cellular machinery to propagate. The replication process involves the transcription of viral genes, some of which, like E66L, are involved in arresting host gene transcription (Ramírez-Medina et al., 2023). The virus's ability to evade host immune responses is facilitated by proteins such as I267L, which inhibits RNA polymerase III-RIG-I-mediated innate immune responses, thereby enhancing viral replication and virulence (Ran et al., 2022). Additionally, the MGF300-2R protein promotes autophagic degradation of host proteins, further aiding in viral replication (Wang t al., 2023).

2.3 Molecular techniques for studying ASFV

Molecular techniques such as the development of recombinant ASFV strains have been pivotal in studying the virus's replication and virulence. For instance, deletion mutants like ASFV-G-ΔA151R and ASFV-G-ΔE66L have been used to assess the roles of specific genes in replication and virulence (Ramírez-Medina et al., 2022; Ramírez-Medina et al., 2023). Transcriptome analysis using RNA-seq has also been employed to profile viral and host gene expression dynamics, providing insights into the molecular interactions during ASFV infection (Figure 1) (Lv et al., 2022). These techniques have been instrumental in identifying potential targets for vaccine development and understanding the virus's pathogenic mechanisms (Liu et al., 2023; Li et al., 2023).

In summary, the ASFV genome is complex and encodes numerous genes that contribute to its virulence and replication. Understanding the structure, replication mechanisms, and molecular techniques used to study ASFV is crucial for developing effective control strategies against this devastating virus.

3 Virulence Factors of ASFV

3.1 Identification of key ASFV virulence genes

African swine fever virus (ASFV) is a complex pathogen with a variety of genes contributing to its virulence. Key virulence genes include A238L, which regulates NFκB and NFAT, and A224L, an apoptosis inhibitor, both of which are involved in immune evasion (Gallardo et al., 2018). The I73R gene is another critical virulence-related gene, playing a significant role in down-regulating the host's natural immune response, making it a potential target for vaccine development (Figure 2) (Liu et al., 2023). Additionally, the I267L gene inhibits RNA polymerase III-RIG-I-mediated innate immune responses, further contributing to ASFV's virulence (Ran et al., 2022).

3.2 Mechanisms of immune evasion by ASFV

ASFV employs several strategies to evade the host immune system. The virus can inhibit MHC Class II antigen processing and presentation, thereby avoiding detection by CD8+ T effector cells (Zhu et al., 2019). Proteins such as MGF360-9L and MGF360-10L play roles in immune evasion by degrading key signaling molecules like STAT1 and JAK1, respectively, which are crucial for the activation of interferon responses (Zhang et al., 2022; Li et al., 2023). The DP96R protein suppresses type I interferon production by targeting IRF3, further aiding in immune evasion (Dodantenna et al., 2024).

3.3 Contribution of ASFV structural proteins to pathogenesis

ASFV structural proteins significantly contribute to its pathogenesis. The MGF300-2R protein promotes the autophagic degradation of IKKα and IKKβ, which are involved in inflammatory responses, thereby modulating

the host's immune response and enhancing viral replication (Wang et al., 2023). The pMGF505-7R protein inhibits IL-1β and type I IFN production by interacting with components of the NF-κB signaling pathway and the NLRP3 inflammasome, which are essential for initiating antiviral responses (Li et al., 2021). These structural proteins are crucial for ASFV's ability to cause disease and evade host defenses.

In summary, ASFV's virulence is mediated by a combination of specific genes and structural proteins that enable the virus to evade the host's immune system and enhance its pathogenicity. Understanding these factors is essential for developing effective vaccines and therapeutic strategies against ASFV.

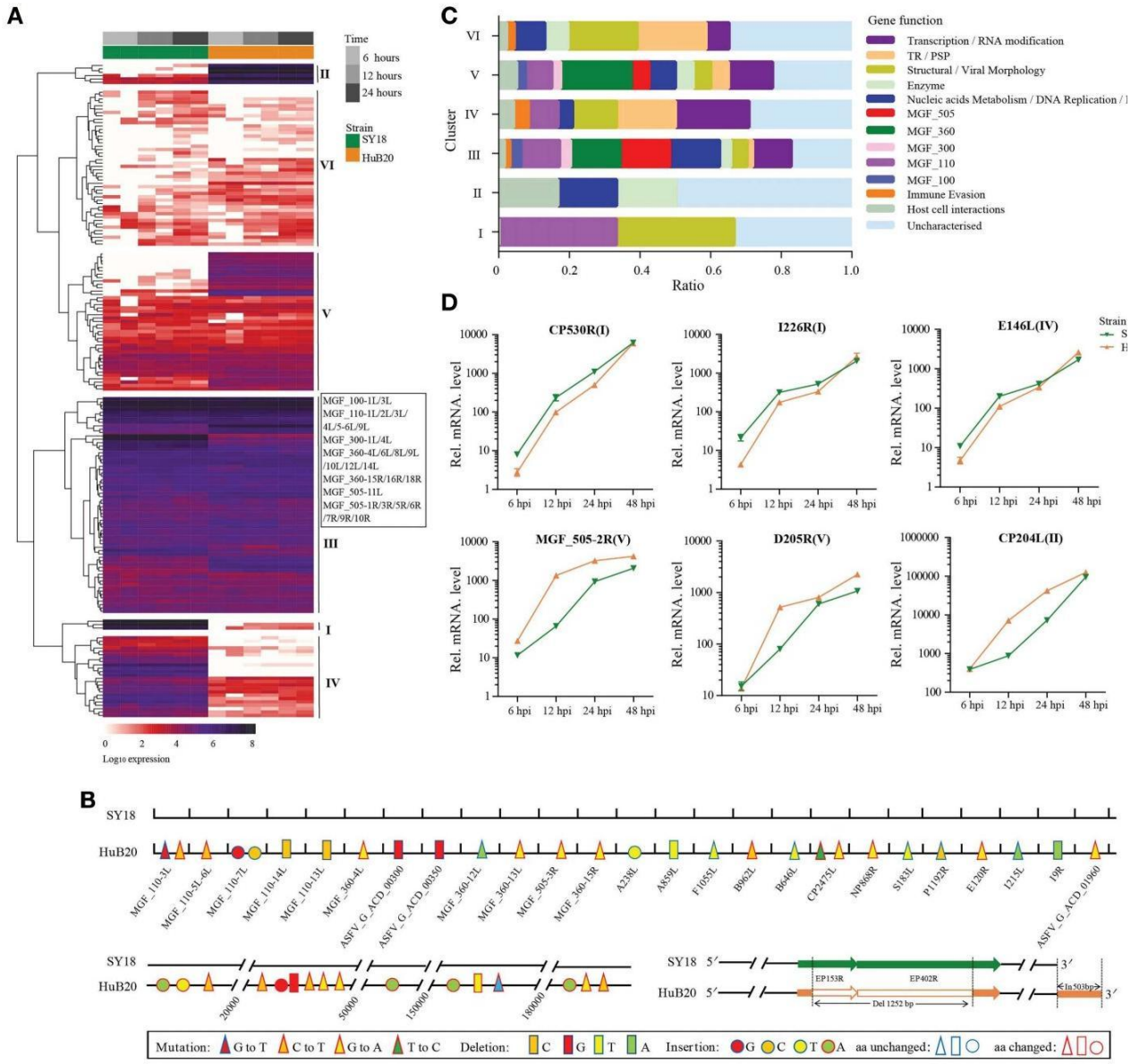

Figure 2 Expression analysis and functional classification of ASFV genes (Adopted from Lv et al., 2022)

Image caption: (A) Heatmap shows the expression levels for the 184 viral genes in the ASFV SY18 and HuB20 strains. (B) Nucleotide mutations, deletions and insertions in ORFs and the noncoding regions between ASFV SY18 and HuB20 genomes. (C) The functional classification of the detected 184 ASFV genes in SY18 and HuB20 strains, annotated with the most enriched function and divided into 6 clusters. (D) Validation of randomly selected ASFV gene expression by real-time PCR. At 6, 12, 24, and 48 hours after PAMs were infected with ASFV SY18 and HuB20 strain (MOI= 3), the transcriptional level of CP530R, I226R, E146L (highly expressed in the SY18 strain infected group) and MGF_505-2-R, D205R, CP204L (highly expressed in the HuB20 strain infected group) were detected by RT-qPCR. The fold-difference was measured by the 2-DDCt method. The RNA levels were normalized to the corresponding b-actin (Adopted from Lv et al., 2022)

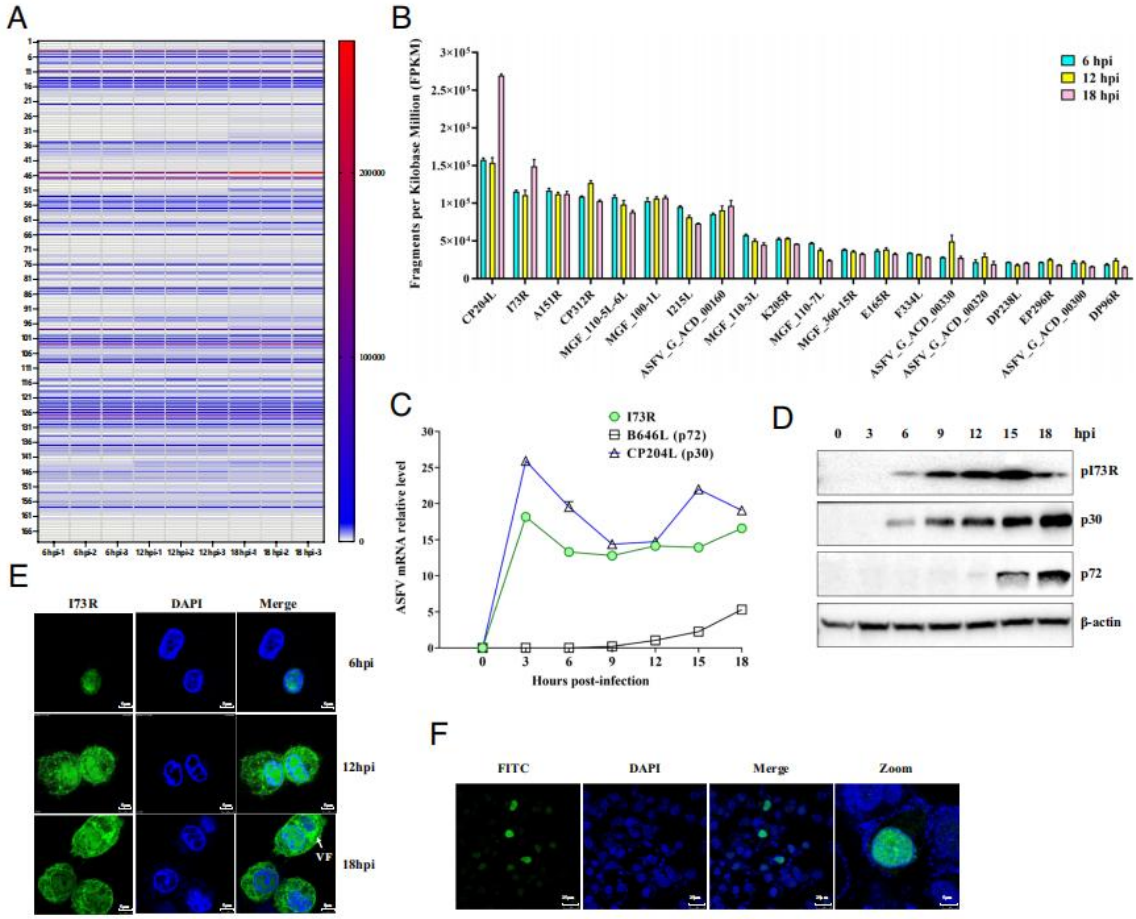

Figure 2 Characteristics of ASFV pI73R. I73R is a conserved gene and is transcribed and expressed in the early stage of the ASFV replication cycle (Adopted from Liu et al., 2023)

Image caption: (A) Heatmap demonstrating the clustering of transcriptional patterns of the ASFV genome at various time points. The abundance of ASFV transcripts was expressed as fragments per kilobase million (FPKM) and indicated using a color key (blue and red correspond to decreased and increased transcriptional levels, respectively). Each column represents one sample, while each row represents the results of hierarchical clustering. (B) The transcript levels of the top 20 genes during ASFV replication. (C) The transcriptional levels of the I73R gene at various time points. The RNAs encoding the open reading frames of I73RB646L, and CP204L were isolated from BMDMs infected with ASFV-GZ at 3, 6, 9, 12, 15, and 18 h postinfection. (D) The protein expression levels at various time points. BMDMs were infected with ASFV-GZ at an m.o.i of 1 for 0, 3, 6, 9, 12, 15, and 18 h. The expression levels of pI73R, p72 and p30 were detected using anti-pI73R, anti-p72 and anti-p30 antibodies, respectively. β-actin was used as the loading control. (E) Subcellular localization of pI73R in BMDMs during ASFV infection. BMDMs were infected with ASFV-GZ (m.o.i = 1) for 6, 12, and 18 hpi and reacted with anti-pI73R monoclonal antibodies and Alexa 488-conjugated goat anti-mouse IgG secondary antibody (green). The nuclei were stained with DAPI (blue) (63×). Note: White arrows indicate the location of the cellular virus factories (VF) formed after ASFV infection. (F) Subcellular localization of pI73R in HeLa cells. HeLa cells were transfected with recombinant pI73R-Flag plasmid and probed with anti-Flag antibodies. The nucleus were stained with DAPI. Green fluorescent protein (GFP) (pseudocolored in green), DAPI (pseudocolored in blue) images were captured using a confocal microscope (63×) (Adopted from Liu et al., 2023)

4 Molecular Mechanisms Underlying ASFV Virulence

4.1 Immune modulation by ASFV virulence genes

African swine fever virus (ASFV) employs various strategies to modulate the host immune response, which is crucial for its virulence. The virus encodes several genes that interfere with host immune signaling pathways. For instance, the A238L gene regulates NFκB and NFAT pathways, which are critical for immune response modulation (Gallardo et al., 2018). Additionally, the MGF360-9L gene antagonizes the JAK/STAT signaling

pathway by degrading STAT1 and STAT (Lv et al., 2022), thereby inhibiting interferon (IFN)-β signaling, which is essential for antiviral defense. The I267L gene further impairs the RNA polymerase III-RIG-I-mediated innate immune response, highlighting its role as a significant virulence factor (Ran et al., 2022; Zhang et al., 2022).

4.2 Interaction of ASFV with host apoptotic pathways

ASFV has developed mechanisms to manipulate host apoptotic pathways to enhance its survival and replication. The A179L gene, a BCL-2 family protein, plays a pivotal role in inhibiting apoptosis by binding to pro-apoptotic proteins, thus preventing cell death and allowing prolonged virus replication. Interestingly, while A179L suppresses apoptosis, it enhances necroptosis, a form of programmed cell death, which may be a strategy to modulate host cell death pathways to the virus's advantage (Shi et al., 2021). The deletion of A179L results in increased apoptosis and reduced virus spread, indicating its critical role in ASFV virulence (Reis et al., 2023).

4.3 Case study: role of the A179L gene in ASFV virulence

The A179L gene is a key player in ASFV's ability to evade host defenses and maintain virulence. Studies have shown that deletion of the A179L gene from the ASFV genome leads to increased apoptosis in infected macrophages, which in turn reduces virus replication and spread. This gene's role in suppressing apoptosis while enhancing necroptosis suggests a complex interaction with host cell death pathways, which may be exploited to develop attenuated vaccines (Shi et al., 2021). Pigs infected with an A179L-deleted virus showed reduced clinical symptoms and lower viremia, although they were not fully protected against subsequent challenges with the virulent parental virus, underscoring the gene's importance in ASFV pathogenicity (Reis et al., 2023).

In summary, ASFV employs a range of molecular mechanisms to modulate host immune responses and apoptotic pathways, with genes like A238L, MGF360-9L, I267L, and A179L playing crucial roles in its virulence. Understanding these interactions provides insights into potential targets for vaccine development and therapeutic interventions.

5 Genetic Variation and Virulence

5.1 Genetic diversity across ASFV strains

African swine fever virus (ASFV) exhibits significant genetic diversity, which is reflected in the variation of its virulence and pathogenicity across different strains. The ASFV genome is large and complex, encoding over 150 genes, many of which have not been fully characterized (Ramírez-Medina et al., 2022). This genetic diversity is evident in the differential expression of viral genes and the host's response to infection. For instance, a study comparing highly virulent and low virulent ASFV strains revealed distinct expression programs and host immune responses, highlighting the genetic variability among strains (Lv et al., 2022). Additionally, the deletion of specific virulence-associated genes, such as those in the multigene family (MGF), can lead to attenuated phenotypes, further illustrating the genetic diversity and its impact on virulence (Wang et al., 2023; Sun et al., 2024).

5.2 Influence of mutations on ASFV virulence

Mutations in ASFV genes can significantly influence the virus's virulence. For example, the deletion of the A151R gene in the ASFV Georgia 2010 isolate resulted in a marked reduction in virulence, as pigs infected with the mutant strain exhibited lower virus titers and milder symptoms compared to those infected with the wild-type virus (Ramírez-Medina et al., 2022). Similarly, the deletion of the DP96R gene, which is involved in suppressing the host's interferon response, has been shown to attenuate the virus, although the precise molecular mechanisms remain to be fully elucidated (Ramírez-Medina et al., 2019; Dodantenna et al., 2024) 3. These findings underscore the critical role of specific genetic mutations in modulating ASFV virulence and highlight potential targets for vaccine development.

5.3 Genotype-specific virulence and pathogenicity

ASFV strains exhibit genotype-specific differences in virulence and pathogenicity, which are influenced by the presence or absence of certain virulence genes. For instance, the I73R gene has been identified as a critical virulence factor, with its deletion leading to a significant reduction in pathogenicity, making it a potential target

for live-attenuated vaccine development (Liu et al., 2023). Additionally, the MGF300-2R and MGF-360-10L genes have been implicated in modulating the host's immune response, with their deletion resulting in reduced virulence and enhanced immune activation in infected pigs (Li et al., 2023; Wang et al., 2023). These genotype-specific differences highlight the complexity of ASFV pathogenicity and the importance of understanding the genetic basis of virulence for effective control and prevention strategies.

In summary, the genetic diversity of ASFV strains, the influence of specific mutations, and genotype-specific virulence factors all play crucial roles in determining the pathogenicity of the virus. Understanding these aspects is essential for developing effective vaccines and control measures against ASFV.

6 ASFV and Host Resistance Mechanisms

6.1 The role of innate immunity in ASFV resistance

The innate immune system plays a crucial role in the initial defense against African swine fever virus (ASFV) infection. ASFV has developed several strategies to evade the host's innate immune responses. For instance, the ASFV gene DP96R suppresses type I interferon (IFN) production by targeting interferon regulatory factor 3 (IRF3), thereby inhibiting the antiviral immune response4. Similarly, the ASFV gene MGF_360-4L impairs interferon signaling by degrading MDA (Sun et al., 2024), a key molecule in the innate immune response, through the recruitment of the mitochondrial selective autophagy receptor SQSTM (Gallardo et al., 2018). Another virulence factor, I267L, inhibits RNA polymerase III-RIG-I-mediated innate immune responses, further demonstrating ASFV's ability to subvert host defenses (Ran et al., 2022). These mechanisms highlight the virus's capacity to modulate host innate immunity, which is critical for its virulence and persistence.

6.2 Adaptive immune response to ASFV

The adaptive immune response, particularly the humoral and cellular components, is essential for controlling ASFV infection. While the specific adaptive immune mechanisms against ASFV are not fully elucidated in the provided data, it is known that the virus can modulate antigen presentation and immune recognition. For example, the ASFV gene EP153R modulates MHC-I antigen presentation, potentially affecting the host's ability to mount an effective adaptive immune response. The development of live attenuated vaccines, such as those lacking specific virulence genes, aims to enhance the adaptive immune response by allowing the host to recognize and respond to the virus more effectively (Gallardo et al., 2018; Liu et al., 2023).

6.3 Host genetic factors in ASFV resistance

Host genetic factors significantly influence the resistance to ASFV. Genetic variations can affect the expression and function of immune-related genes, thereby impacting the host's ability to respond to ASFV infection. Although specific host genetic factors related to ASFV resistance are not detailed in the provided data, studies on other pathogens suggest that genes involved in interferon signaling and immune regulation could play a role (Ciancanelli et al., 2016). Understanding these genetic factors is crucial for developing strategies to enhance resistance in domestic pigs, potentially through selective breeding or genetic engineering.

In summary, ASFV employs various strategies to evade the host's innate and adaptive immune responses, with specific viral genes playing pivotal roles in modulating these defenses. Host genetic factors also contribute to the variability in resistance to ASFV, highlighting the complexity of host-pathogen interactions in ASFV infections.

7 Diagnostic and Therapeutic Implications

7.1 Current diagnostic methods for ASFV detection

Current diagnostic methods for African swine fever virus (ASFV) detection primarily rely on molecular techniques such as real-time PCR assays. These assays are designed to target specific ASFV genes, such as the MGF505-7R gene, which has been shown to enhance ASFV virulence and pathogenesis. The TaqMan-based real-time PCR method developed for the MGF505-7R gene is both sensitive and specific, capable of detecting ASFV-infected samples at an early stage with high accuracy (Qi et al., 2023). This method provides a rapid and reliable tool for ASFV screening and monitoring, crucial for controlling outbreaks.

7.2 Potential biomarkers for virulence assessment

Identifying potential biomarkers for ASFV virulence is essential for understanding the virus's pathogenicity and developing effective vaccines. Several ASFV genes have been identified as virulence factors, including MGF360-9L, which antagonizes the JAK/STAT signaling pathway, and DP96R, which suppresses type I IFN production by targeting IRF3. The deletion of these genes in experimental vaccine strains has shown to attenuate the virus, suggesting their potential as biomarkers for assessing ASFV virulence (Zhang et al., 2022; Sun et al., 2024). Additionally, the ASFV MGF505-7R gene is considered a candidate for vaccine formulations due to its role in enhancing virulence.

7.3 Vaccine development and antiviral strategies

Vaccine development for ASFV is focused on creating live attenuated vaccines by deleting specific virulence-associated genes. For instance, the deletion of the I73R gene has been shown to produce a potent live-attenuated vaccine candidate1. Similarly, the removal of genes such as A137R, MGF360, and MGF505 has been explored to reduce virulence and enhance safety in vaccine strains (O'Donnell et al., 2015; Koltsov et al., 2024). These strategies aim to balance attenuation with immunogenicity to provide effective protection against ASFV. Moreover, the development of DIVA (Differentiating Infected from Vaccinated Animals) vaccines, which include antigenic markers like the p11.5 protein, is a promising approach to distinguish between infected and vaccinated animals, facilitating better disease management.

In summary, advancements in diagnostic methods, identification of virulence biomarkers, and innovative vaccine development strategies are crucial for controlling ASFV. These efforts aim to improve early detection, assess virulence accurately, and provide effective immunization against this devastating virus.

8 Concluding Remarks

Recent studies have significantly advanced our understanding of the virulence mechanisms of African swine fever virus (ASFV). Key virulence genes such as A151R, DP96R, and MGF300-2R have been identified as critical players in the virus's ability to evade host immune responses and maintain its pathogenicity. The A151R gene, for instance, is involved in virus virulence in domestic swine, and its deletion results in reduced virulence, suggesting potential for vaccine development1. Similarly, the DP96R gene suppresses type I interferon production by targeting IRF3, highlighting its role in immune evasion. The MGF300-2R gene promotes autophagic degradation of key immune signaling proteins, further elucidating ASFV's strategy to suppress host immune responses. These insights into ASFV's molecular interactions with host cells provide a foundation for developing targeted interventions.

Future research should focus on further characterizing the molecular interactions between ASFV and host immune pathways. Investigating the roles of other virulence-associated genes, such as I73R and MGF_360-4L, which have shown potential in attenuating the virus and enhancing immune responses, could lead to the development of effective live-attenuated vaccines. Additionally, exploring the differential expression of host genes in response to ASFV infection, as demonstrated in transcriptome analyses, could uncover new therapeutic targets and improve our understanding of ASFV pathogenicity. Collaborative efforts in genomics and immunology will be crucial in advancing ASFV control strategies.

The control of ASFV is of paramount importance due to its devastating impact on the global swine industry and associated economic losses. Effective ASFV control measures, including the development of vaccines targeting key virulence genes, could significantly reduce the spread of the virus and its economic burden. Moreover, understanding ASFV's immune evasion strategies can inform public health policies and biosecurity measures to prevent outbreaks. The integration of scientific research with policy-making will be essential in mitigating the public health and economic impacts of ASFV.

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Conflict of Interest Disclosure

The author affirms that this research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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