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Role of genetic factors in different swine breeds exhibiting varying levels of resistance/susceptibility to PRRSV

Xiangbin You [a,b,1], Gan Li [a,b,1], Ying Lei [a,b], Zhiqian Xu [a,b], Ping Zhang [a,b], Youbing Yang [a,b,*]

[a] College of Animal Science and Technology, Henan University of Science and Technology, Luoyang 471023, China
[b] Luoyang Key Laboratory of Animal Genetics and Breeding, Luoyang 471023, China

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ABSTRACT

Porcine reproductive and respiratory syndrome (PRRS), caused by the PRRS virus (PRRSV), is an economically significant contagious disease. Traditional approaches based on vaccines or medicines were challenging to control PRRSV due to the diversity of viruses. Different breeds of pigs infected with PRRSV have been reported to have different immune responses. However, due to the complexity of interaction mechanism between host and PRRSV, the genetic mechanism leading to PRRSV susceptibility/resistance in various pig breeds is still unclear. Herein, the role of host genetic components in PRRSV susceptibility is systematically described, and the molecular mechanisms by which host genetic factors such as SNPs, cytokines, receptor molecules, intestinal flora, and non-coding RNAs regulate PRRSV susceptibility/resistance. Therefore, improving the resistance to disease of individual animals through disease-resistance breeding technology is of profound significance for uplifting the sustainable and healthy development of the pig industry.

1. Introduction

Porcine reproductive and respiratory syndrome (PRRS) is recognized as one of the viral infectious diseases with a substantial economic impact on the pig industry throughout the world. It significantly damages pigs at all stages, such as slowing the growth of fattening pigs, leading to premature birth and miscarriage of sows, and a decrease in the quality of boar semen (Darwich et al., 2011; Olanratmanee et al., 2015). The causative agent of disease is a small, single-stranded positive-stranded RNA virus that was first isolated in the Netherlands in 1991 (Lelystad virus) (Wensvoort et al., 1991). Subsequently, a similar virus was isolated in the USA (Benfield et al., 1992; Collins et al., 1992). PRRS was first reported in China in 1995, named CH-1a, which confirmed the existence of PRRSV in China (Guo et al., 2018). In 2006, there was a large-scale outbreak of a disease called "high fever" with unknown etiology in China. Basically, it was caused by the mutant PRRS virus (PRRSV), later named highly pathogenic PRRSV (HP-PRRSV). The PRRSV NADC30-like strain has been widely circulating in China since 2012 (Li et al., 2016). In 2017, the NADC34-like PRRSV strain originating in the United States was again found in China (Bao and Li, 2021).

PRRSV belongs to the genus Arteritis virus in the Arteritis Virus family, a spherical capsular virus, 45–65 nm in diameter, with fibroids on the surface of the capsule, relatively smooth, and can grow on porcine alveolar macrophages (PAMs) (Dokland, 2010). PRRSV has two strains of different serotypes. North American type is VR-2332 strain (PRRSV-2), while the European type is Lelystad virus (PRRSV-1). Nucleotide similarity of these two PRRSVs is 55%−70%, and the amino acid similarity is 50%−80% (Darwich et al., 2011). PRRSV genome size is approximately 15.4 kb, with a cap structure (5′-Cap) at the 5′ end, a polyadenine nucleotide tail structure (3′-polyA) at the 3′ end, and at least 10 open reading frames (ORFs) of 1a, 1b, 2a, 2b, 3, 4, 5, 5a, 6, 7, respectively. There are overlapping areas between adjacent ORFs.

Both PRRSV-1 and PRRSV-2 are circulating, and approximately 80% of pig farms are seropositive for PRRSV (Guo et al., 2018). Currently, most vaccines are modified live viruses against PRRSV-1, and some viruses that control PRRSV-2. They protect homologous parental strains and partly xenostrains. There are also significant safety issues with weakened vaccines, such as high mutation rates that lead to virulence reversals and recombination between vaccines and wild-type strains (Wang et al., 2016; Wei et al., 2013). Conversely, mass administration of live attenuated vaccines can lead to safety problems and more genetic differentiation (Mengeling et al., 1999; Zhou et al., 2014). Based on the

* Corresponding author.
E-mail address: 9906133@haust.edu.cn (Y. Yang).
[1] These authors contributed equally to the paper as first authors.

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in-depth study of PRRSV, researchers are trying to find a novel vaccine development strategy that must be safe, and efficient, and protect different PRRSV strains in a broad-spectrum way. At the same time, other approaches to effectively control PRRS are being explored, including building effective biosecurity defenses and breeding PRRSV-resistant pig breeds.

Resistance/susceptibility of different populations and individuals to the same pathogen infection are diverse. Herein, we focus on the evidence of host genetic factors in resistance/susceptibility to PRRS. Meanwhile, the molecular mechanisms of SNPs, cytokines, PRRSV receptors, and non-coding RNA affecting PRRSV susceptibility in pigs were also reviewed. Therefore, the use of disease-resistant breeding technology to improve the disease resistance of individual animals is of profound significance in expanding the sustainable and healthy development of pig industry.

2. Different pig breeds have different resistance/susceptibility to PRRSV

Role of genetic factors in the differences in resistance/susceptibility to PRRS between breeds has been studied for many years. As early as 1998, Halbur et al. (1998) found differences in the susceptibility of Duroc, Hampshire, and Meishan pigs to VR2385, a high-virulence strain of PRRSV. Ait-Ali et al. isolated alveolar macrophages from 5 different breeds (Large White, Pietrain, Landrace, Synthetic B, and Synthetic E) of pigs and infected them with PRRSV in vitro. The results showed that the accumulation level of PRRSV RNA in Landrace swine PAMs was significantly lower than in other breeds (Ait-Ali et al., 2007). In the summer of 2006, a massive and devastating PRRS outbreak occurred in about 10 provinces of China, infecting more than 2 million pigs and causing the death of at least 400,000 animals (Tian et al., 2007). However, some indigenous Chinese pig breeds strongly resisted to PRRSV infection, and only a few individuals died. Zhou et al. (2011). reported that infection of different breeds of Landrace and Large White was observed on a pig farm in Hubei province, with high mortality. However, the native Chinese breed Tongcheng pigs showed mild symptoms and did not die of PRRSV infection Xing et al. also report that DLY (Duroc × Landrace × Yorkshire) pigs exhibited various clinical features that typify the disease. Conversely, the Dapulian pigs (a Chinese indigenous pig breed) showed only mild signs of disease (Xing et al., 2014). These studies indicate the presence of a host genetic component in PRRSV disease susceptibility and the need for further studies to identify the cellular mechanisms influencing disease susceptibility. To study the relationship between PRRS resistance/susceptibility and host genetics, PRRS Host Genetics Consortium (PHGC) was established in the United States in 2007 (Lunney et al., 2011). Understanding the mechanism of PRRSV susceptibility in different pig breeds from perspective of host genetics is conducive to cultivating PRRS-resistant pigs, increasing the resistance of pigs to PRRS, increasing the growth rate of pigs, and providing help with animal welfare.

Generally speaking, environmental factors, nutritional and health status of pigs, virulence of PRRSV, and other factors affect the susceptibility of different pig breeds to PRRSV (Lunney and Chen, 2010). For the host, researchers proposed the concepts of resistance and tolerance. Resistance can be defined as the ability of an individual host to resist infection or control the life cycle of a pathogen (Lunney and Chen, 2010; Rowland et al., 2012). For example, Christopher-Hennings et al. found that the average days of PRRSV shedding in the semen of Landrace, Yorkshire, and Hampshire pigs were 51±26.9 days, 7.5 ± 4.9 days, and 28.3 ± 17.5 days, respectively (Christopher-Hennings et al., 2001). Bates et al. evaluated the susceptibility to PRRSV in Hampshire × Duroc cross-breed pigs and Nebraska Index line pigs and found that all PRRSV-challenged pigs were infected. However, pigs with a weak response to PRRSV were found to have faster virus clearance beginning at 7 and 14 dpi, which meant there was less viremia, In contrast, pigs that responded strongly to PRRSV continued to increase viremia from 4 to 14 days (Bates et al., 2008). Tolerance can be defined as the ability of the host to tolerate infection and show little or no measurable detriment, that is, minimal effects of the disease (Lunney and Chen, 2010; Rowland et al., 2012). Previous studies have used highly pathogenic PRRSV to infect Tibetan pigs, ZangMei black and Large White, and compared the susceptibility of three pig breeds to PRRSV. The results showed that typical clinical symptoms such as cough, diarrhea and high fever were unobserved in the attacked Tibetan pigs. However, all symptoms occur in large white pigs, with a mortality rate of about 40% (3/8) (Kang et al., 2016). Increased PRRS resistance or tolerance in pigs will have significant economic and welfare implications for the global swine industry. However, identifying genes or pathways that determine PRRSV resistance/susceptibility in different breeds of pig is a complex process. Fortunately, some progress has been made, especially in breeding PRRSV-resistant pigs by processing PRRSV receptors.

3. Genetic mechanism of the difference in PRRSV susceptibility between pig breeds

3.1. Cytokines play a role in the susceptibility of swine to PRRSV

After PRRSV infection, host's innate and acquired immune functions are enhanced to resist infection by pathogenic microorganisms, and cytokines play an essential role in initiating and regulating immune responses. Innate immune cytokines such as IFN, TNF-a, IL-10, and IL-6 play an important role in the PRRSV infection process. Previous studies have shown that TNF-a and type I interferon can directly inhibit viral replication (Wang et al., 2021). Xing et al. showed that PRRSV-susceptible Duroc × Landrace × Yorkshire pigs have lower serum IFN-c levels than PRRSV-resistant Dapulian pigs (Xing et al., 2014). Ait-Ail et al. showed that PRRSV replication was consistently higher in Large White, Synthetic B, Pietrain, and Synthetic E pigs than in the Landrace pigs. With the exception for 16 h, TNF-a expression levels were significantly different at all time points after 2 h. And TNF-a expression levels in synthetic B, Pietrain, and Landrace were markedly higher than those in Large White and Synthetic E (Ait-Ali et al., 2007). Additionally, acquired immune-related cytokines play a more critical role in the PRRSV immune response, especially cytokines released by CD4+ Th1 cells and CD4+ Th2 cells (Elenkov, 2008). Kang et al. showed that the expression level of IL-10 increased significantly in the early (4-day post-infection, DPI) stage of PRRSV infection in PRRSV-resistant Tibetan pigs and ZangMei black pigs, but decreased rapidly to a normal level in the middle (7 DPI) and late (14 DPI) stage of PRRSV infection. However, the expression level of IL-10 in PRRSV-susceptible Large White pigs was not significantly increased (Kang et al., 2016). These results suggest that cytokine synthesis and secretion play a vital role in the differential mechanism of PRRS susceptibility among pig breeds. Pig breeds with strong resistance to PRRSV had higher levels of cytokine expression. PRRSV infection is easy to cause an inflammatory response in the host, IFN, TNF, some interleukins, etc., play an influential role in virus clearance during infection. However, PRRSV infection only induces poor innate and adaptive immune responses, leading to incomplete virus clearance in pigs and persistent infection, which is generally believed to be due to significant innate immunosuppression and delayed humoral immunity. In addition, abnormally high cytokines expression under PRRSV infection can cause some tissue and organ damage. They suggest that severe tissue injury rather than uncontrolled infection may determine the fatal outcomes of HP-PRRSV infection (Han et al., 2014).

3.2. The PRRSV receptor plays a decisive role in the susceptibility of different breeds of pig

The process of viral infection includes viral adhesion, host cell endocytosis, and genome release (Nauwynck et al., 1999). Recognition of specific cell receptors is critical in PRRSV infection, and successful viral entry depends on receptor utilization. Molecular receptors such as

heparan sulfate, vimentin, CD151, CD163, CD169, and CD209 have been confirmed to be essential for PRRSV infection in the host (Zhang and Yoo, 2015).

Among them, CD163 is considered the primary and core receptor of PRRSV and determines cellular sensitivity to the virus (Johnsson et al., 2018; Prather et al., 2017). Pigs that are completely naturally resistant to PRRS have not yet been found. Interestingly, the researchers used gene editing technology to knock out CD163 and generated CD163 knockout pigs, which were found completely resistant to PRRSV infection (Whitworth et al., 2016). CD163, a member of the cysteine-rich scavenger receptor (SRCR) superfamily, has 17 exons and 9 extracellular SRCR domains, of which SRCR domain 5 encoded by exon 7 plays an essential role in PRRSV susceptibility (Wang et al., 2019). Researchers used CRISPR technology to delete the entire CD163 SRCR5 or 41 aa in the SRCR5 domain, and the resulting gene-edited pigs were resistant to PRRSV (Burkard et al., 2018; Guo et al., 2019). On the contrary, some PRRSV non-insensitive cell lines, such as BHK-21, PK-0809, and NLFK, were susceptible to PRRSV after CD163 overexpression and produced high virus titers (Calvert et al., 2007). Furthermore, Meng et al. found that CD163 mRNA expression levels were significantly higher in Jiangquhai pig PAMs at the early stage of PRRSV infection. They believe this may be why Jiangquhai pigs have high resistance to PRRSV (Meng et al., 2018).

Sialoadhesin is a macrophage-restricted lectin that binds to sialic acid and is also known to as CD169 or siglec-1. Intact N-terminal domain in CD169 is considered necessary and sufficient to bind and internalize PRRSV in cultured macrophages (An et al., 2010). Studies have found that porcine Pk-15 cells that do not express CD169 (derived from porcine kidneys) have low sensitivity to PRRSV, but when PK-15 cells are transfected with CD169, these cells can internalize PRRSV (Vanderheijden et al., 2003). However, Delputte et al. found that CD169 knockdown did not prevent PRRSV infection (Delputte et al., 2011). Interestingly, when CD169 and CD163 were co-expressed in previously nonpermissive cells, viral production was 10 to 100 times higher than the expression of CD163 alone (Van Gorp et al., 2008). This suggests that CD169 may not be necessary for PRRSV infection, but may play an important auxiliary role in the PRRSV infection process.

CD151 is a tetraspanin superfamily member with various cellular functions, including cell signaling, cell activation, and platelet aggregation (Fitter et al., 1999). Some studies have found that BHK-21 cells are susceptible to PRRSV infection after transfection with CD151. On the contrary, transfection of CD151 siRNA inhibited PRRSV infection in Marc-145 cells (Shanmukhappa et al., 2007).

3.3. One SNP leads to individual/breed differences in susceptibility/resistance to PRRS

Genetic polymorphism is the cause of population diversity and single nucleotide polymorphism (SNP) plays a crucial role in host susceptibility or resistance to viral diseases (Kenney et al., 2017). Gene variations associated with resistance to particular infections often involve virus entry receptors, co-receptors, or receptor-modifying enzymes. Like the CD163 and CD169 receptors in pigs. Dong et al. found that natural genetic variations in CD163, CD169, and RGS16 genes were associated with resistance to PRRSV or PCV2b or both infections. The identified SNPs can be selected to increase natural resistance to PRRSV or PRRSV-PCV2b or both co-infections (Dong et al., 2021a). Additionally, regression analysis of recovered pigs, sick pigs, dead pigs, and healthy pigs showed that the risk of disease in 5 genotypes with four SNPs (CD169–G1640T GT genotype, CD169–C1654A AA genotype, CD169–C4175T CC and CT genotypes, and CD163–A2552G AA genotype) of CD163 and CD169 was significantly lower than that in other genotypes. SNPs in CD169 G1640T and CD169 C1654A may lead to the substitution of Arg547Leu and Leu552Ile in CD169, which is associated with the formation of disulfide bond and is critical to the natural conformation and stability of protein (Ren et al., 2012). Other studies have shown that the pig CD163 gene with CC genotype (c.*146C>T) showed significantly higher nucleocapsid-specific antibody titer at 11 days post-challenge (Niu et al., 2016).

A quantitative trait locus associated with PRRS virus resistance/susceptibility was found on chromosome 4 of Sus scrofa. A further study found that this region (1 Mb region) was associated with higher levels of viremia and lower weight gain after PRRSV infection. Many single nucleotide polymorphisms (SNP) in this ~1 Mb region are in very high linkage disequilibrium, making identifying of the causal mutation difficult. WUR10000125 (WUR) SNP is used as the marker SNP of this area. Boddicker et al. (2014a), (2014b). Interestingly, marker-assisted selection based on WUR genotypes (or in conjunction with another candidate SNPS) not only improves host response to PRRS, but also improves co-infection of PRRSV with PCV2b or other pathogens (Dunkelberger et al., 2017a, 2017b). Significantly, SSC4 QTLs were associated with responses to different PRRSV isolates (Hess et al., 2016; Waide et al., 2017). In this region, a large number of genes were found to be associated with pig resistance to PRRSV infection, including members of the guanosine binding protein (GBP) family (GBP1, GBP2, GBP4, GBP5, and GBP6), CCBL2, GTF2B and PKN2 (Boddicker et al., 2012; Kommadath et al., 2017). GBP5 was identified as a major gene for host response to PRRS (Dong et al., 2021b; Schroyen et al., 2016). WUR and GBP5 SNP were found to have a high but incomplete linkage imbalance ($r^2 = 0.94$) (Jeon et al., 2021). An intron SNP rs340943904 in GBP5 is a strong candidate causal mutation of SSC4 QTL, which controls changes in host response to PRRSV (Koltes et al., 2015). Previous studies have shown that the higher resistance in the pigs heterozygous for the WUR and GBP5 markers could be mediated by increased antiviral cytokine (IFN-α) production and T cell activation(Khatun et al., 2020a).Interferon-induced gene GBP1 has been implicated in innate immune responses to bacterial and viral infections (Kim et al., 2011). Niu et al. showed that an SNP in exon 2 of GBP1 was associated with more significant viremia and lower body weight gain after PRRSV infection (Niu et al., 2016). Polymorphisms in gene exons lead to amino acid substitutions that affect the molecular polarity and conformation of the protein, negatively impacting other production traits such as growth and meat quality. Gol et al. also reported that due to an SNP ($A>G$) of GBP1 3′UTR, the expression level of GBP1 in the liver and tonsil of individuals carrying allele A was significantly higher than that of individuals carrying allele G (Gol et al., 2015). Different alleles affect the transcriptional splicing of GBP1, leading to the differential expression of GBP1 in various individuals. These genes are significantly associated with resistance PRRSV, and can also be induced by enhanced antiviral cytokines (IFNα) and T cell-mediated immune responses (Khatun et al., 2020a). Additionally, genome-wide association analysis of two genetic lines experimentally infected with PRRSV by Walker et al. showed that the regions SSC7 and SSC17 accounted for 1.2% of the genetic variation of PRRSV-specific antibodies in serum or lung (Walker et al., 2019).

Genetic polymorphisms in various genes associated with innate and adaptive immune responses to antiviral infection in the host are also strongly associated with host susceptibility/resistance to the virus. Myxovirus resistance (Mx) proteins belong to the dynamin superfamily and are important innate host defense RNA viruses. The study by Li et al. reported that a short interspersed repetitive element insertion polymorphism in the porcine MX1 promoter is associated with PRRSV resistance in pigs (Li et al., 2015). Several studies have shown that the polymorphism of the FUT1 gene is correlated with the resistance/-susceptibility of different hosts to bacteria and viruses (Hesselager et al., 2016; Li et al., 2018). After natural infection with PRRSV and haemophilus parasuis, pigs with the GG or AG FUT1 gene had a higher relative risk of morbidity than pigs with the AA FUT1 gene genotype (Wang et al., 2012).

3.4. Non-coding RNAs also play an essential role in PRRSV susceptibility

About half of the DNA in higher organisms is transcribed as RNA, the

vast majority of which is non-coding RNAs (ncRNA). Non-coding RNA (ncRNA) refers to RNA that does not encode proteins. These include RNAs with known functions, such as long non-coding RNA, circRNA, siRNA, and microRNA, and RNAs with unknown functions (Matsui and Corey, 2017). There are thousands of unique ncRNA sequences within cells. Over the past decade, research has transformed our view of ncRNAs from "junk" transcripts to functional regulatory molecules that mediate cellular processes, including chromatin remodeling, transcription, post-transcriptional modification, and signal transduction (Anastasiadou et al., 2018). Therefore, aberrant regulation of ncRNA is often associated with various diseases. Many studies have shown that PRRSV infection can change the expression of ncRNA, which also plays a role in the PRRSV infection process. Previously, Zhang et al. reported that downregulation of miR-218 by PRRSV facilitates viral replication by inhibiting type I interferon responses (Zhang et al., 2021). The PRRSV infection upregulates the expression of miR-382–5p, which inhibits polyI: C-induced type I interferon production targeting heat shock protein 60 (HSP60), thus promoting PRRSV replication in Marc-145 cells (Chang et al., 2020). Zhang et al. also found that long non-coding RNA LNC_000397 negatively regulates PRRSV replication by inducing interferon-stimulated genes (Zhang et al., 2022).

Past studies have also found that non-coding RNA is widely involved in plants' and animals' susceptibility or antiviral immunity. In our previous study, we investigated the role of miRNAs in the infection and susceptibility of PRRSV, twenty-four miRNA libraries were constructed and sequenced from PRRSV-infected and mock-infected PAMs of Meishan, Landrace, Pietrain, and Qingping pigs at 9 h post-infection (hpi), 36 hpi and 60 hpi. MiRNA let-7 family, mir-331–3p, mir-210 and long non-coding RNA NEAT1 are significantly differentially expressed in different pig breeds, which play an enssential role in the regulation of susceptibility in various pig breeds (You et al., 2022, 2020). To elucidate differences in PRRSV resistance between the two varieties, Zhen et al. used RNA-seq to identify differentially expressed non-coding RNAs in response to PRRSV in Tongcheng and Large White PAMs (Zhen et al., 2018). These studies found that many differentially expressed miRNAs, such as miR-331–3p, differentially expressed in four pig breeds, could significantly inhibit PRRSV replication in vitro and in vivo (You et al., 2020). These non-coding RNA expression data may also aid in identification of genetic variants that may be used to identify candidate genes for PRRSV resistance or tolerance.

3.5. *Quantity and relative abundance of gut microbiota influence swine susceptibility to PRRSV*

Gut microbiome is a group of bacteria, archaea, fungi, protozoa, and viruses that live in the gut. It is influenced by many factors, including genetics, stress, diet, antibiotics, and more (Gibson and Roberfroid, 1995). From a genetic perspective, the study found significant differences in the number and abundance of gut microbes among different hosts. Few studies have also found differences in *Firmicutes* and *Bacteroidetes* in the fecal bacterial community of varying pig breeds. For example, *Firmicutes* accounted for 70.4%, and *Bacteroidetes* accounted for 14.4% of Jinhua pig feces in China. While Duroc, Yorkshire and Landrace pig feces accounted for 39.6%, 42.0%, and 45.6% of *Firmicutes*, and 57.0%, 51.4%, and 47.6% of *Bacteroidetes* (Pajarillo et al., 2014, 2015; Yang et al., 2018). Moreover, the gut microbiome is essential in maintaining gut homeostasis, innate immunity, and susceptibility to infectious diseases. Zhang et al. transplanted the fecal microbiota of wild pigs and domestic pigs into weaned piglets. They challenged them with attenuated African swine fever virus (ASFV) strains and found significantly milder clinical symptoms and fewer viral loads were observed. In contrast, pigs transplanted with wild pigs fecal from were challenged intramuscularly with attenuated ASFV strains than pigs transplanted with fecal from domestic pigs (Zhang et al., 2020). The diversity and abundance of gut microbiota also affect host susceptibility/resistance to PRRSV. As reported by Wang et al., the quantity and relative abundance of probiotics positively affect host immunity and growth performance, which is also responsible for individual resistance to pathogens. Conversely, high levels of pathogenic bacteria in susceptible individuals were associated with poorer clinical outcomes. For example, the relative abundance of *Campylobacter* in the gut of susceptible pigs was three times higher than that of resistant pigs at 7 dpi, and the degree of diarrhea in susceptible pigs was significantly higher than in resistant pigs. *Parabacteroides, Christensenellaceae-R7-group,* and *Anaerotruncus* were positively correlated with viral load and negatively associated with weight gain (Wang et al., 2022). Gut microbiota has been confirmed to be closely related to host health. Currently, the mechanism of the gut microbiota and PRRSV susceptibility in different breeds of pig is unclear, which is worthy of further exploration.

4. Conclusions and perspectives

Disease is an essential factor affecting the development of livestock and poultry industry. In the production process, traditional methods such as strengthening management and using drugs are used mainly to solve the disease problem, but this cannot fundamentally control and solve the disease epidemic. Long-term sustainability of farm animal production will depend on having animals with an adequate level of resistance to infectious diseases. The industry needs to develop more effective means to control infectious diseases, not only because of these economic losses, but also because of public pressure to reduce the use of antibiotics, improve animal welfare and improve food safety. The occurrence of disease is related to genetics and environment, so individuals with higher disease resistance (because of underlying genetic mechanisms) can be selected from a genetic perspective to improve the overall population disease resistance. This has led breeders to shift their focus from production and performance traits to more comprehensive breeding, including disease resistance and welfare measures (Fig. 1).

In the past few decades, marker-assisted selection (MAS) has been widely studied, which can improve varieties by selecting resistant genes and effectively carrying out breeding for disease resistance (Hagely et al., 2020). The MAS is a method of breeding selection based on the molecular level, mainly on the main genes for disease resistance. For example, SNPs associated with PRRSV susceptibility in different pig breeds were screened at the DNA level (Khatun et al., 2020b; Sun et al., 2012). A large number of SNPs were found to be associated with PRRSV susceptibility, including immune genes, PRRSV receptor genes, and other related genes. In addition, candidate genes associated with the susceptibility of different pig breeds were also identified by gene expression analysis at the RNA and protein levels. Breeding pigs with a particular trait is a slow process that requires multiple rounds of crossing and backcrossing to penetrate each gene and can take many years. But with gene editing technology, it is possible to change or remove specific genes in a single generation of animals.Recently, gene-editing technology has been successfully used to generate antiviral pigs, which offers the possibility of increasing animal disease tolerance and improving animal economic traits in the future. Gene editing technology also provides a possible way to simultaneously obtain multiple beneficial genotypes within one generation without affecting other superior phenotypes. Double-gene-knockout pigs generated in the study by Xu et al. were resistant to both PRRSV and TEGV and exhibited reduced sensitivity to PDCoV while maintaining the same growth and reproductive traits as wild-type pigs (Xu et al., 2020).

Intestinal microbiota plays an important role in pig health and production, which has been widely recognized by researchers in recent years. Metabolism-related bioactive molecules and bacterial molecular components produced by intestinal flora are important components for host cells to carry out essential physiological activities, and also have a profound impact on normal immune responses or immune disorders. There are differences in the composition and fraction of intestinal microbiota in different pig breeds, which provides a new direction for studying the differences in susceptibility/resistance of PRRSV in

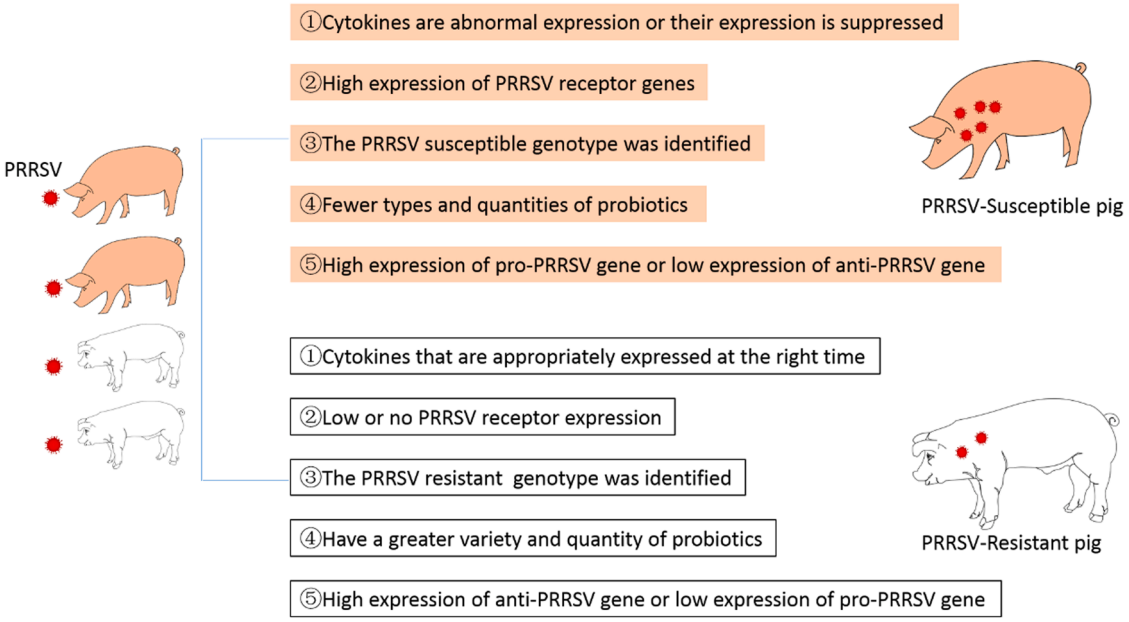

Fig. 1. Potential molecular mechanisms in PRRSV-resistant and PRRSV-susceptible pigs.

different pig breeds.

CRediT authorship contribution statement

Xiangbin You: Conceptualization, Data curation, Funding acquisition, Software, Writing – original draft, Writing – review & editing. **Gan Li:** Conceptualization, Writing – original draft. **Ying Lei:** Funding acquisition, Software, Writing – review & editing. **Zhiqian Xu:** Software, Writing – review & editing. **Ping Zhang:** Writing – review & editing. **Youbing Yang:** Conceptualization, Funding acquisition.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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