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PRRSV Vaccine: Challenges and Prospective

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Abstract

Since porcine reproductive and respiratory syndrome virus (PRRSV) emerged in the late 1980s, it had spread to become the one of the most economically important viral pathogens affecting swine production worldwide. Although PRRSV vaccines have been commercially available and widely used for over 20 years, the vaccination has been shown limited role in control and eradication of the virus. In this review, we summarized recent advances in PRRSV vaccines, including modified live-attenuated PRRSV vaccines (PRRSV-MLV), PRRS killed-virus (KV) vaccines and experimental PRRS vaccines. Challenges associated with existing vaccines and future directions for the development of better PRRSV vaccines are discussed.

Keywords: PRRSV, PRRSV-MLV, PRRS KV, Advances, Challenges

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Introduction

Prcine reproductive and respiratory syndrome (PRRS) was first reported in the North America in 1987 and appeared in Europe in 1990 (Terpstra et al., 1991; Wensvoort et al., 1991; Collins et al., 1992; Rossow,1998). Subsequently, PRRS expanded and had been found worldwide. The disease causes reproductive failure, respiratory disease, and growth retardation in the pigs, which lead to huge economic losses for the swine industry globally (Neumann et al., 2005).

The causative agent, PRRS virus (PRRSV) is an enveloped positive-strand RNA virus classified in the order Nidovirales, family Arteriviridae, and genus Arterivirus (Snijder and Meulenberg, 1998). PRRSV have evolved at a high evolutionary rate (order of 10^{-2} /site/year) compared with those (orders of 10^{-3} to 10^{-5}/site/year) of standard RNA viruses, which promotes extensive antigenic and genetic variation (Hanada et al., 2005). There are two well-known PRRSV genotypes: Type 1 (European) which contains at least 3 subtypes and Type 2 (North American) which contains at least 9 distinct genetic lineages (Wensvoort et al., 1991; Mardassi et al., 1994). Both genotypes of PRRSV share an approximately 60% nucleotide sequence homology to each other (van Woensel et al., 1998; Forsberg, 2005). Within each genotype, the virus isolates can exhibit up to 20% variability of nucleotide sequences (Forsberg, 2005). It is a big challenge for the experts in PRRS research or vaccine industry scientists to develop a broadly protective vaccine against genetically diverse PRRSVs in the field.

The ideal PRRS vaccine should possess following characters, i.e. rapid induction of immunity, protection against most currently prevalent PRRSV strains, no adverse outcomes to swine health and ability to differentiate vaccinated from infected animals (Rock, 2007). However, no vaccine is commercially available that meet all of the above criteria till now. PRRSV modified-live vaccines (PRRSV-MLV) always has safety concerns and lack of cross-protection. PRRS killed virus (KV) vaccine, on the other hand, is safe but confers limited protection against either homologous or heterologous virus. Apparently, development of better PRRSV vaccines and more efficient vaccination strategies are urgently needed. Fortunately, novel techniques for developing next generation vaccines, adjuvants and vaccine delivery systems are emerging. In this review, progress and challenges for current PRRSV vaccines are reviewed. New insights to guide future efforts to develop better PRRS vaccines are provided.

PRRSV vaccines and their challenges

Modified live attenuated PRRSV vaccine

Since the first commercially available modified live-attenuated PRRSV vaccine (PRRSV-MLV) was released in the United States in 1994, several PRRSV-MLVs have been licensed in PRRS endemic countries (Nan et al, 2017). Currently, PRRSV-MLVs are still the main options available on PRRSV endemic swine farms to control PRRSV (Nan et al, 2017). However, the efficacy and safety are big concerns and challenges of current PRRSV-MLVs. For efficacy concerns: 1) PRRSV-MLVs elicit relatively weak humoral and cell-mediated immune (CMI) response (Diaz et al., 2006; Zuckermann et al., 2007). The PRRSV-specific neutralizing antibodies (NA) which is responsible for clearance of PRRSV from the pigs only appear 4 wks after vaccination and have relatively low titer (usually between 8-32) (Darwich L, et al., 2010). T

cell response to PRRSV-MLVs appears 2-4 wks and peaks at 32 wks after vaccination, which is extremely delayed compared with T cell response to other RNA viruses, such as pseudorabies virus (PRV) MLV vaccine (appears within 1 wk of vaccination and peaks approximately at 4 wk after vaccination) (Meier WA et al., 2003); 2) PRRSV-MLVs could confer effective protection against genetically homologous wild type PRRSVs, while conferring only partial protection or no protection against heterologous PRRSVs (Charerntantanakul, 2012; Roca et al., 2012).

For safety concern: 1) the first issue is reversion to virulence through genetic mutations of the vaccine virus and/or recombination with field virulent PRRSV (Murtaugh MP, et al. Virus Res 2010; 154: 18-30). Both China and United States have reported that field isolates from PRRSV outbreaks exhibited nearly identical nucleotide sequences to the vaccine strain (Botner et al., 1997; Wang et al., 2010). Vaccine-like and vaccine-derived PRRSV isolates have been reported to cause diseases in pigs as well (Opriessnig et al., 2002; Key et al., 2003); 2) It has been reported that PRRSV-MLV vaccinated pigs can develop viremia for up to 4 wks after immunization, which could lead to spread of vaccine virus to naive animals (Charerntantanakul, 2012; Wang et al., 2013); 3) PRRSV-MLVs could induce antibody-dependent enhancement (ADE) of infection (Jiang et al., 2003; Zhou et al., 2004).

Apparently, currently commercial PRRSV-MLVs are not satisfied. However, due to its immunogenic potentials, lots of efforts have been put to develop safer and more efficient PRRSV-MLVs by using modern biotechnologies. Further attenuation with full evaluation is one of these strategies. JXA1-R, a genetically stable, live attenuated vaccine strain against HP-PRRSV, was widely used throughout China. In our study, we found that pigs vaccinated with JXA1-R (attenuated Chinese highly pathogenic PRRSV vaccine) developed broadly neutralizing antibodies with high titers to JXA1-R, HV-PRRSV and heterologous NA PRRSV strain NADC-20. In addition, we also found that IFN-α and IFN-β occurred at higher levels in the lungs of pigs vaccinated with JXA1-R (Galliher-Beckley et al., 2015). Chimeric PRRSV is one of the approaches to broaden cross-protection. Several PRRSV infectious cDNA clones have been constructed by using reverse genetic techniques, what made it possible for the PRRSV-MLVs to swapping gene segments from heterologous PRRSV strains. Recent studies demonstrated that chimeric PRRSVs constructed by shuffling two or more structural genes exhibiting improved cross-protective efficacy against multiple heterologous strains (Zhou et al., 2013, Tian et al., 2017). The computationally designed and synthesized infectious clone which contains common antigen-coding sequence among heterologous PRRSV strains could be useful and holds great promise for development of universial vaccines against PRRSV in the future (Vu et al., 2015; Nan Y, et al., 2017).

PRRS killed-virus vaccine

Efficacious PRRS killed-virus (KV) vaccine is warranted for the control and eradication of PRRS. Since the early 1990s, researchers have been attempting to develop PRRS KV vaccines. Currently, PRRS KV vaccine is licensed for use worldwide, but not in the Unites States (Charerntantanakul, 2012). The PRRS KV vaccine is considered safe and could help PRRSV-positive pigs to increase PRRSV specific antibody and CMI responses (Bassaganya-Riera, et al., 2004; Kim et al., 2011). However, naïve pigs do not elicit detectable PRRSV-specific antibodies (neither non-NA nor NA) (Kim et al., 2011) and lack of CMI responses when vaccinated with PRRSV KV vaccine (Bassaganya-Riera et al., 2004; Piras et al., 2005). Repeated administration of PRRSV KV vaccine could boost anti-PRRSV immunity and CMI responses of pigs. However, the boosted humoral and cellular responses are not satisfied for protective efficacy (Papatsiros, et al. 2006; Zuckermann, et al., 2007; Nilubol D, et al., 2004).

Undoubtedly, it is critical to improving humoral and cellular responses of PRRSV KV vaccine. Up to now, several promising attempts have been reported for developing efficacious PRRS KV vaccines. Such as incorporation of suitable adjuvants in PRRSV KV vaccine to accelerate and magnify immune responses to PRRS KV vaccines (Karniychuk, et al., 2012; Vanhee, et al., 2009; Charerntantanakul., 2009) and using nanoparticle-based PRRS KV vaccine delivery system to induce superior cross-protective immunity against PRRSV (Dwivedi , et al., 2012; Dwivedi , et al., 2013; Binjawadagi, et al., 2014a; Binjawadagi, et al., 2014b). Depending on these findings, special formulations or antigen delivery systems combined with novel adjuvants may enhance the immune response to PRRS KV vaccines, which ignites hope to control or eradicate PRRS by using PRRS KV vaccines in the near future.

Experimental PRRS vaccines

In addition to PRRS MLVs and KVs, numerous efforts have been made to develop other types of PRRS vaccine. These experimental PRRS vaccines include DNA vaccine, subunit vaccine, plant-derived vaccine, and vector vaccine. Most of these experimental PRRS vaccines either showed limited protection in pigs or have not been fully evaluated in pigs. For example, pigs immunized with a GP5 Mosaic T-cell DNA vaccine could develop PRRSV specific antibodies and IFN-γ mRNA expression, but still cannot confer full protection (Cui et al., 2016). Subunit vaccines (baculovirus-expressed or plant-expressed PRRSV structural proteins) could induce anti-PRRSV specific antibodies in pigs, but the limited duration and level of immunity, and the inability to induce heterologous protection may limit the effectiveness of subunit vaccines (Plana Duran et al., 1997; Chia et al., 2011; Renukaradhya et al., 2015). Vector vaccines (adenoviral vector and poxvirus vector based) could offer the advantage of eliciting both cell-mediated and humoral immune responses. Mice immunized with adenovirus-based PRRSV vaccine exhibited high viral NA titers and strong lymphocyte proliferation responses, but have not been tested in pigs (Gagnon et al., 2003; Jiang et al., 2008). Pigs immunized with poxvirus vector-based PRRSV vaccines had significantly lower body temperatures, lower levels of viremia and viral RNA load compared to the control pigs when challenged with virulent PRRSV, but did not receive complete protection (Shen et al., 2007; Zheng et al., 2007).

DIVA (differentiation of infected and vaccinated animals) PRRS vaccine

The availability of a DIVA vaccine is very important for the surveillance, control and eradication of PRRS. Subunit vaccine has its inherent ability to be used as a DIVA vaccine. However, no definitive protective antigen has been identified for the PRRSV and the efficacy of subunit vaccines is not satisfactory. Another strategy to investigate a DIVA PRRS vaccine is to use deletions in the Nsp2 gene, which resulted in the easy differentiation of vaccine and wild-type-exposed animals by serology using an ELISA or molecularly using RT-PCR. However, no data was presented for their efficacy, because there was no challenge in these studies (de Lima, et al. 2008; Fang, et al., 2008; Kim, et al., 2009). Recently, the A2MC2-P90, an attenuated strain of the first reported strain (A2MC2) with strong ability to induce IFN synthesis (Nan et al., 2012; Wang et al., 2013), was developed and evaluated in pig challenge study. The presented data suggest that A2MC2-P90 might be used as a promising DIVA PRRS vaccine candidate due to its unique features, such as ability to induce IFNs, induce higher levels of NAs in pigs, avirulence in pigs and holds nsp2 deletion (181 amino acid residues) (Nan et al., 2012;Wang et al., 2013 ,Ma et al., 2016, Ma et al., 2017, Fontanella et al., 2017).

Conclusion and perspectives

Three decades have passed since the emergence of PRRS. Though

massive efforts have been put in vaccine research, no PRRS vaccine is available to meet the standards (set in the meeting "Colloquium on Prospects for Development of an Effective PRRS Virus Vaccine" in 2007) for an ideal vaccine. Concerns about safety and less efficacy against heterologous reinfection of PRRSV-MLVs have persisted. Current PRRSV-MLVs are only labelled for use in PRRS-positive swine herds, and are not recommended for naïve herds. Experimental PRRS vaccines (DNA vaccine, subunit vaccine, and vector vaccine) are still far from ready for practical application. By the growing push to consider regional elimination or eradication of PRRSV, the development for more robust efficacy and broader heterologous cross-protection PRRS KV vaccines is urgently needed. Further understanding how PRRSV causes disease (environment, virus and host immunity) combining new technologies (novel adjuvants or immunomodulators, inactivation methods, nanoparticles and other alternative delivery systems) could help to achieve this goal.

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Declaration of interest

The authors declare that they have no competing interests.

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