Vaccine against CSFV

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Classical swine fever (CSF), caused by CSF virus (CSFV), is one of the most devastating viral epizootic diseases of swine in many countries. To control the disease, highly efficacious and safe live attenuated vaccines have been used for decades. However, the main drawback of these conventional vaccines is the lack of differentiability of infected from vaccinated animals (DIVA concept). Advances in biotechnology and our detailed knowledge of multiple basic science disciplines have facilitated the development of effective and safer DIVA vaccines to control CSF.

classical swine fever DIVA concept vaccine

1. Introduction

Classical swine fever (CSF) is a highly contagious, economically significant, multi-systemic viral disease in swine [1], which is notifiable to the World Organization for Animal Health (OIE). The causative agent, CSF virus (CSFV), is an enveloped, positive-sense, single-stranded RNA virus. It belongs to the *Pestivirus* genus within the Flaviviridae family [2]. Other members of this genus are bovine viral diarrhea virus (BVDV) 1 and 2, border disease virus (BDV), and an increasing number of tentative pestivirus species [3][4]. According to the recent reclassification of *Pestivirus* genus by the International Committee on Taxonomy of Viruses (ICTV), BVDV-1 is re-designated as Pestivirus A, BVDV-2 is re-designated as Pestivirus B, CSFV is re-designated as Pestivirus C, BDV is re-designated as Pestivirus D, and many of tentative *Pestivirus* species are re-designated as Pestivirus E-K [5].The CSFV genome encodes a precursor polyprotein of 3898 amino acids (aa), which is post-translationally processed into four structural proteins (C, E^{rns}, E1 and E2) and eight non-structural proteins (N^{pro}, p7, non-structural protein [NS] 2, NS3, NS4A, NS4B, NS5A, and NS5B) by cellular and viral proteases [6][7]. Antibodies against the envelope glycoproteins E2, E^{rns}, and NS3 have been detected in pigs that recover from infection [8][9]. The major immunogen is the glycoprotein E2, in terms of inducing neutralizing antibodies and protection against future infection [9][10].

CSF has consistently caused important economic losses to the pig industry since its emergence [11][12]. Several countries have succeeded in eliminating CSF following the implementation of strict control measures. However, in most parts of the world with significant pig production, CSF is at least sporadically present. To date, CSF remains endemic in South and Central America, Eastern Europe, and neighboring countries, and Asia. Little is known about the African situation. The most recent outbreaks have been reported in Korea, Colombia, Russia, Brazil, and Japan [13]. In particular, the reemergence of CSF from previously CSF-free Japan in September 2018 has caught much attention [14][15]. Thus, CSFV remains an endemic and reemerging virus in pigs and continues to threaten pork production worldwide and the food security of populations in developing countries.

Systematic vaccination and non-vaccination stamping-out are the two main strategies to control CSF [16][17]. In CSF-free zones, or where eradication is in progress, control is based on the non-vaccination and strict stamping-out policy. In contrast, due to the enormous costs of stamping-out, systematic prophylactic vaccination is a more effective strategy for CSF control in CSF endemic countries. As with many other viral infections affecting livestock, several highly efficacious live attenuated CSF vaccines have been widely used for decades and have paved the way to successful eradications in many areas. However, the use of these vaccines interferes with the serological diagnosis, as they lack differentiability of infected from vaccinated animals (DIVA). Indeed, due to the trade restrictions that are imposed on pigs vaccinated with conventional live attenuated vaccines, only DIVA vaccines are considered a feasible option for future control and eradication of CSF. Therefore, the development of potent DIVA vaccines poses a challenge for research groups worldwide. So far, different concepts have been investigated during the development of CSFV DIVA vaccines, including vector vaccines, recombinant attenuated vaccines with chimeric constructs, subunit vaccines, peptide vaccines, and RNA/DNA vaccines. This review is aimed at describing progress and challenges associated with CSFV vaccine development, revealing the strategies and approaches that may also be helpful for the development of next-generation vaccines against other pathogens.

2. Conventional Live Attenuated Vaccines and Their Application

In the early 20th century, the primary vaccines against CSF were developed, which consist of the virus and porcine hyperimmune serum, followed by the crystal-violet vaccine [18]. However, the safety and efficacy of these vaccines were poor. Further investigations aimed at the development of live attenuated vaccines were performed in rabbits since the 1940s [19][20]. During that time, the Chinese vaccine strain (C-strain), the so-called Chinese hog cholera lapinized virus (HCLV), was widely used in both mainland China and many other countries due to its better safety and efficacy than other strains [21]. In addition to passage through rabbits, researchers also tried other methods to attenuate CSFV. For instance, the low-temperature-adapted Japanese guinea-pig exaltation-negative (GPE^-) strain [22][23] and the French cell culture-adapted Thiverval strain were obtained [24][25]. Nowadays, the most commonly used strains are the C-strain, the lapinized Philippines Coronel (LPC) strain, the GPE^- strain, the Thiverval strain, and their derivative strains [26][27].

The C-strain was developed jointly by the China Institute of Veterinary Drugs Control and the Harbin Veterinary Research Institute in China in 1956 [28]. It was developed by attenuating a highly virulent strain through at least 480 passages in rabbits [28]. The strain spread worldwide. At present, many commercial strains were derived from the C-strain, such as Pestiffa (French), VADIMUN (USA), and Riems (Germany), which have also been widely used. The C-strain formulations used in both China and Europe indicate that reliable protection is provided as early as 72 or 96 h after a single vaccination [29][30][31]. Immunity can persist for at least 6–18 months and even be lifelong [30][32]. Studies targeting the genetic stability of the C-strain proved that the vaccine is highly stable [30]. In addition, the C-strain is safe in young piglets or pregnant sows, even in immunosuppressed individuals [33]. In addition, inoculation of the vaccine confers complete protection against CSFV isolates from all three genotypes [34]. Likewise, the commercial LPC, GPE^-, and Thiverval vaccines show similar performance as C-strain vaccines.

In addition to the wide use of C-strain as injection vaccine for most domestic pigs, it can also be used as oral vaccine for wild boars and domestic pigs in rural areas [35][36]. Indeed, oral vaccination with the C-strain was proved to be safe and effective [37][38]. Recently, an oral formulation of the C-strain was improved. Researchers have reported oral baits obtained by absorption of C-strain onto bread followed by lyophilization. While the current commercial oral vaccine bait containing liquid C-strain vaccine requires storage at −20 °C, this new oral bait is stable for 18 months at 4 °C. Pigs vaccinated with these new oral baits displayed seroconversion after 14 days [39]. Thus, the new formulation provides a more cost-effective method to improve vaccination of domestic pigs and wild boars.

The requirements of the ideal vaccine postulated by Terpstra and Kroese [40] mainly regard safety, efficacy, and marketability. For CSFV, live attenuated vaccines have long been considered to meet all the requirements. Nevertheless, a recent outbreak that occurred in a previously CSF-free island applying live attenuated low-virulence strain of Miyagi (LOM) vaccine inoculation led to a later study showing that the employed LOM strain can cause viremia and cross the placenta to piglets [41][42]. This research reminds us of the need to recharacterize the safety of the live attenuated vaccines using more recent technologies. In addition, another main drawback of the live attenuated vaccines is the lack of a serological marker concept [26][43][44] that would allow differentiation of infected from vaccinated animals (DIVA concept). Due to the trade restrictions that are imposed on pigs vaccinated with conventional live attenuated vaccines, the development of novel potent vaccines combined with the DIVA concept becomes more and more important.

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