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Review

Recent advances in the development of recombinant vaccines against classical swine fever virus: Cellular responses also play a role in protection

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Abstract

Classical swine fever virus (CSFV) is the causative agent of one of the most devastating porcine haemorrhagic viral diseases, classical swine fever (CSF). CSFV mainly infects endothelial cells and macrophages and at the same time promotes bystander apoptosis of the surrounding T cells, causing strong immune suppression and high mortality rates. Most animals experience acute infection, during which they either die or survive by producing neutralising antibodies to the virus. However, in a few cases, the impaired immune system cannot control viral progression, leading to chronic infection.

Efficient live attenuated vaccines against CSFV exist and are routinely used only in endemic countries. The ability of these vaccines to replicate in the host, even at very low rates, makes it extremely difficult to distinguish vaccinated from infected animals, favouring a restricted policy regarding vaccination against CSFV in non-endemic countries. There is a clear need for efficient and safer marker vaccines to assist in the control of future CSF outbreaks. In this review article, some of the most recent advances in the field of recombinant vaccines against CSFV are presented and the nature of the protective immune responses they induce is discussed.

Keywords: CSFV; Vaccine; Neutralising antibodies; T cell response; Immune suppression

Introduction

Classical swine fever (CSF) or hog cholera is a highly infectious viral disease included in the list of diseases notifiable to the OIE (www.oie.int). It affects domestic and wild pigs and is considered to be one of the most devastating diseases for the pig industry throughout the world from both the economic and sanitary point of view (Moennig et al., 2003).

In vivo, CSF virus (CSFV), the aetiological agent of CSF, targets the porcine immune system, mainly those cells derived from the monocyte-macrophage lineage, inducing marked bystander apoptosis of non-infected surrounding lymphocytes, by mechanisms still not totally understood (Summerfield et al., 1998a, 2001). Highly virulent strains of CSFV cause marked immune suppression and high mortality (Susa et al., 1992; Lee et al., 1999; Gomez-Villamandos et al., 2003). The clinical signs of the disease depend not only on the specific strain of the virus, but also on many other factors, such as the age and the immune status of the animals (Moennig et al., 2003).

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The global distribution of CSF has been extensively reviewed (Frías-Lepoureau and Greiser-Wilke, 2002; Greiser-Wilke and Moennig, 2004; Dong and Chen, 2007). The disease is endemic in Asia and is prevalent in many countries of central and South America. Several outbreaks have been reported in Caribbean countries in recent years (Frías-Lepoureau, 2002; de Arce et al., 2005; Pereda et al., 2005). Little is known about the situation in Africa, where CSF has been reported in Madagascar, and recently in South Africa (Sandvik et al., 2005).

While CSF was eradicated from North America several decades ago, a progressive eradication programme has been implemented in the European Union (EU) since the early 1990s. This programme is based on a non-vaccination policy, the culling of infected animals or those in contact with infected herds (stamping out) and the restriction of animal movements or their products. Vaccination is only allowed in emergencies (European Union, 1980). However, in spite of control programmes, the virus has been introduced periodically into the EU via wild pigs or foreign imports, as occurred during the 1990s in Belgium, Germany, The Netherlands, Spain and Italy and, since 2000, in the UK, Spain and Germany (Paton and Greiser-Wilke, 2003; Dong and Chen, 2007).

As with many other diseases affecting livestock, the most efficient vaccines currently available against CSFV are live attenuated vaccines that were developed more than 50 years ago (de Smit et al., 2000). Although guaranteeing high protection rates, the live attenuated vaccines against CSF have some disadvantages. For example, vaccination with live attenuated viruses elicits similar antibody patterns to those observed in naturally infected animals, making it extremely difficult to differentiate vaccinated animals from infected ones. Recent advances in vaccination strategies have circumvented this dilemma by the use marker or DIVA (differentiation of infected from vaccinated animals) vaccines (van Oirschot, 1999; de Smit, 2000).

Despite recent efforts to develop new and safer marker vaccines against CSFV, along with improved diagnostic tools, there is still a need for further improvements (Floegel-Niesmann, 2001; Greiser-Wilke and Moennig, 2004). This review covers some of the most relevant advances in this field. However, further efforts to understand the immune mechanisms relevant to CSFV protection and to improve diagnostic tools are required to develop safer marker vaccines against this important disease.

Immune response induced by CSFV infection in pigs

Understanding the interaction of CSFV with the cells of the porcine immune system and its role in viral pathogenesis is a key point in designing new antiviral strategies. Work carried out several decades ago described the capacity of CSFV to destroy the lymphoid follicles (Cheville and Mengeling, 1969) and these results have subsequently been confirmed (Pauly et al., 1998). Among the main targets for CSFV are bone marrow cells from the monocyte-macrophage linage ($SWC3^+$; $SWC8^-$). Interestingly, while mature granulocytes ($SWC3^+$; $SWC8^+$) are not susceptible to CSFV infection, the virus does infect the less differentiated myeloid progenitor cells ($SWC3^{low}$; $SWC8^-$), thus explaining the presence of CSFV in peripheral blood mature $SWC8^+$ cells (Summerfield et al., 1998a, 2001).

Despite the high mortality and the severity of lesions in animals with virulent CSFV, one peculiarity of CSFV infection is that most infected cells in the bone marrow remain healthy, while surrounding uninfected cells succumb, mainly due to bystander apoptosis. This is most probably due to soluble factors secreted by the infected cells (Summerfield et al., 2001).

Infected pigs show marked immune suppression, with an altered population of T cells and depletion of lymphocytes (van Oirschot et al., 1983), mainly $CD4^+$ and $CD8^+$ T cells. Depending on the virulence of the viral strain, pigs can have as much as 90% of their total T cells depleted in the final stages of the disease (Pauly et al., 1998). This effect can be observed as early as one day after infection, even before viraemia has been established (Summerfield et al., 1998b). Immunosuppression can be detected much earlier than seroconversion and clinical signs of the disease, which is relevant both for early diagnosis and for the study of viral pathogenesis (Pauly et al., 1998; Summerfield et al., 1998a, 2000; Ganges et al., 2005).

As with many other severe haemorrhagic diseases, CSFV infects endothelial cells (Avirutnan et al., 1998; Yang et al., 1998). These cells seem to play a key role in CSFV pathogenesis, which is characterised by the development of microthrombi, disseminated intravascular coagulation and fibrinolysis, among other clinical signs (Summerfield et al., 2000). While CSFV infection of endothelial cells suppresses both interferon production and apoptosis, it induces inflammatory cytokines (Campos et al., 2004).

CSFV exploits the migratory capacity of macrophages and dendritic cells (DCs) for dissemination throughout the body (Carrasco et al., 2004). Activation of anti-apoptotic pathways in infected cells ensures virus survival, whereas induction of the expression of soluble pro-inflammatory cytokines promotes bystander apoptosis of the surrounding T cells, thus avoiding recognition of the infected cells (Bensaude et al., 2004).

Recent evidence suggests that CSFV might induce immune suppression not only by secreting cytokines, but also by other mechanisms, such as expressing the CSFV structural E^{rns} protein, which has been shown to be toxic for T cell lymphocytes in vitro (Bruschke et al., 1997; Pauly et al., 1998). CSFV also activates T cells that secrete cytokines, such as IL10, which is probably a key cytokine in the immunosuppression observed after CSF infection (Suradhat et al., 2005). Considering the capacity of CSFV to escape the immune response, strategies must be designed to control the infection and to prevent CSFV-mediated immune evasion.