PRRS Immune Control Strategies

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Porcine reproductive and respiratory syndrome (PRRS) affects farmed pigs worldwide and still causes heavy direct and indirect losses. The syndrome emerged in the late 1980s, in USA, and later on in Europe, and it eventually became enzootic in most countries among farmed pigs. Late-term reproductive failure in sows with transplacental transmission of the virus, preweaning mortality of piglets, respiratory distress, anorexia, and possible cutaneous hyperemia in weaners and growers are common clinical signs of PRRS.

Keywords: pig ; PRRS ; PRRS virus ; immune response ; disease resistance ; disease control

1. Overview

The control of porcine reproductive and respiratory syndrome (PRRS) is still a major issue worldwide in the pig farming sector. Despite extensive research efforts and the practical experience gained so far, the syndrome still severely affects farmed pigs worldwide and challenges established beliefs in veterinary virology and immunology. The clinical and economic repercussions of PRRS are based on concomitant, additive features of the virus pathogenicity, host susceptibility, and the influence of environmental, microbial, and non-microbial stressors. This makes a case for integrated, multi-disciplinary research efforts, in which the three types of contributing factors are critically evaluated toward the development of successful disease control strategies. These efforts could be significantly eased by the definition of reliable markers of disease risk and virus pathogenicity. As for the host's susceptibility to PRRSV infection and disease onset, the roles of both the innate and adaptive immune responses are still ill-defined. In particular, the overt discrepancy between passive and active immunity and the uncertain role of adaptive immunity vis-à-vis established PRRSV infection should prompt the scientific community to develop novel research schemes, in which apparently divergent and contradictory findings could be reconciled and eventually brought into a satisfactory conceptual framework.

2. Porcine Reproductive and Respiratory Syndrome

Porcine reproductive and respiratory syndrome (PRRS) affects farmed pigs worldwide and still causes heavy direct and indirect losses [1]. The syndrome emerged in the late 1980s, in USA, and later on in Europe, and it eventually became enzootic in most countries among farmed pigs. Late-term reproductive failure in sows with transplacental transmission of the virus, preweaning mortality of piglets, respiratory distress, anorexia, and possible cutaneous hyperemia in weaners and growers are common clinical signs of PRRS [2].

The two swine Arteriviruses sustaining PRRS (PRRSV-1 and PRRSV-2) had been previously identified as European (EU) type I, with the first strain isolated in 1991 and named "Lelystad", and the North American (NA) type II, isolated in 1992 with the acronym ATCC VR-2332 [3]. More recently, the two viruses were classified as Betaarterivirus suid 1 and Betaarterivirus suid 2 by the International Committee on Taxonomy of Viruses (https://talk.ictvonline.org, accessed on 6 August 2021).

Whereas PRRS virus (PRRSV) infections are widely prevalent in farmed swine, the repercussions may vary, from asymptomatic, to very serious clinical courses, often depending on pig age and production phase [2]. On the whole, strong experimental and circumstantial evidence shows that the clinical outcome of PRRSV infection is the product of three components: virus virulence, host susceptibility, and environmental stressors [4]. Notably, PRRSV infection gave rise to subclinical courses over several decades, before PRRSV met the highly susceptible, lean type, rapid growth pigs reared in western Europe [4].

Extensive research has led to the development of effective diagnostic procedures, enabling timely detection of the PRRSV genome and antibody [5]. Oral fluids (OF), meat juice, and tissues obtained from the castration and tail-docking of piglets were also validated for large-scale diagnostic surveys [6].

Eradication of PRRS was shown to be possible on the basis of herd closure and strict biosafety control measures [7]; however, the underlying costs, logistics, and infrastructure needed have so far prevented the large-scale adoption of this procedure. Accordingly, the control of PRRS is usually based upon a complex of integrated control measures aimed at "stability", i.e. a condition in which clinical signs of PRRS are absent in the breeding-herd population and PRRSV is no longer transmitted from sows to their offspring [8]. In practice, swine farms aim to co-exist with PRRSV under conditions of minimal clinical fallout and productive losses. In this respect, the prevention of PRRSV infection in suckling piglets is a foundational part of this control strategy, bearing in mind the much higher susceptibility of non-adult pigs to PRRSV [9].

The main risk factors underlying serious clinical outcomes of PRRSV infection are depicted in **Figure 1**. All of them are dealt with in the following sections.

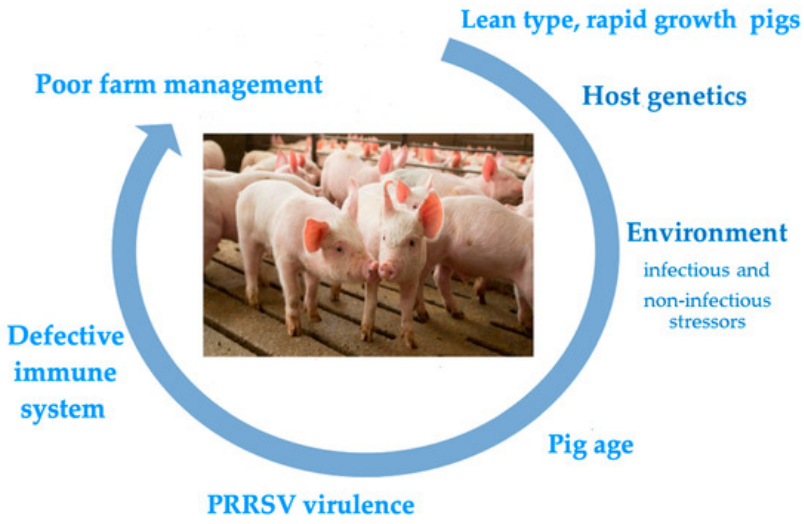

Figure 1. The figure depicts the main risk factors associated with serious clinical outcomes of PRRSV infection in farmed pigs. The rolling circle starts with the lean pig phenotype, which has underlain the clinical history of PRRS since the 1980s. The subsequent risk factors in the figure are not ordered on a time-related or weight basis. Pigs may actually be exposed to multiple risk factors with additive or synergistic final effects.

3. Biosecurity: the Foundation of Successful Disease Control Strategies

After decades of research and field experience, biosecurity is still the foundation of PRRS control on farms, as detailed, for example, in the guidelines of the American Association of Swine Veterinarians (https://www.aasv.org/aasv/PRRSV_BiosecurityManual.pdf, accessed on 3 July 2021). This implies that farm management procedures aim to reduce PRRSV infectious pressure by a proper combination of "all in—all out" protocols; parity control; limitation of cross-fostering; strict forward flow; quarantine for replacement sows and gilts; and large-scale adoption of multi-site production units, where pig groups are channeled throughout distinct production phases, giving rise to the so-called "batch management production systems (BMPS)". These measures have been conducive to improved animal health standards compared with traditional farrow-to-finish herds, because the recirculation of pathogens and microbial infectious pressure can be more easily controlled.

4. Acclimatization as the Second Pillar of Successful Disease Control on the Farm

In addition, PRRS stability demands the successful "acclimatization" of replacement gilts to the PRRSV strains circulating in the farm before the breeding period [10]. Pending a definition of reliable correlates of protection, "acclimatization" should be interpreted as a stepwise process of "adaptation" to field PRRSV strains, in which undefined innate and adaptive immune responses, the down-regulation of permissiveness to PRRSV of pig macrophages [11], and, perhaps, the "education" of macrophages to a better control of inflammatory responses by epigenetic mechanisms [12] concur to obtain a pig population that experiences PRRSV infection without serious clinical outcomes.

5. Which Elements Underlie Successful Disease Control?

In retrospect, the above features related to disease control are definitely sobering. They teach us that (A) the extent of microbial infectious pressure resulting from farm biosafety profiles, and (B) the previous "education" of the immune system are both pivotal to successful disease control.

In a wider perspective that includes the research efforts made so far, four points seem to be of paramount importance for the effective control of PRRS:

The selection of disease-resistant pig phenotypes, differing from the lean type, highly susceptible ones [13]. The high levels of oxidative stress in such pigs [14] are likely to exacerbate the inflammatory responses to infectious and non-infectious stressors and, in particular, the noxious synergism between bacterial LPS and PRRSV infection [15]. This is probably a point of some importance, since LPS can also be inhaled at high concentrations in pig herds [16], and circumstantial evidence on farm showed clinical improvement in PRRSV-infected groups after reduction of animal concentration in outdoor weaning cages. The results of extensive studies on the genetic bases of disease resistance highlighted a single nucleotide polymorphism (SNP) marker that was strongly associated with weight gain and viral load after PRRSV infection, with a possible role of the interferon-induced guanylate-binding protein gene family [17]. Moreover, editing of the CD163 gene in pig zygotes was shown to be a valuable approach for generating PRRSV-resistant animals [18].

Strict application of bio-safety measures toward a substantial reduction of microbial infectious pressure and chronic inflammatory responses, as well as outright “herd closure” strategies aimed at eradication [7].

Higher standards of animal welfare to prevent chronic stress and stress-related immunosuppression [19].

Active immune control, which may, in turn, include two distinct aspects: (A) Development of innate and adaptive immune responses to PRRSV [20]. (B) Reduced permissiveness of macrophages to PRRSV replication as a possible outcome of “trained immunity” [12], and/or of the inflammatory microenvironment affecting the maturation of macrophage precursors [11].

On the whole, the first three points are commonly accepted, and relevant measures are pursued to varying extents in different parts of the world. However, how the immune control of PRRSV takes place is a highly contentious issue, which deserves due attention and, probably, new approaches toward credible translational prospects.

6. Conclusions

The above issues demand evidence-based responses from the scientific community. It goes without saying that such issues pertain to different areas of research and practitioner activities, focusing on improved disease control actions and surveillance.

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