Veterinary Immunology and Immunopathology 167 (2015) 1–14

Contents lists available at ScienceDirect

Veterinary Immunology and Immunopathology

journal homepage: www.elsevier.com/locate/vetimm

Review Paper

Innate and adaptive immunity against Porcine Reproductive and Respiratory Syndrome Virus

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ARTICLE INFO

Article history:
Received 19 March 2015
Received in revised form 29 June 2015
Accepted 1 July 2015

Keywords:
PRRSV
Immunology
Antibody
Cell-mediated immunity
Innate immunity

ABSTRACT

Many highly effective vaccines have been produced against viruses whose virulent infection elicits strong and durable protective immunity. In these cases, characterization of immune effector mechanisms and identification of protective epitopes/immunogens has been informative for the development of successful vaccine programs. Diseases in which the immune system does not rapidly clear the acute infection and/or convalescent immunity does not provide highly effective protection against secondary challenge pose a major hurdle for clinicians and scientists. Porcine reproductive and respiratory syndrome virus (PRRSV) falls primarily into this category, though not entirely. PRRSV causes a prolonged infection, though the host eventually clears the virus. Neutralizing antibodies can provide passive protection when present prior to challenge, though infection can be controlled in the absence of detectable neutralizing antibodies. In addition, primed pigs (through natural exposure or vaccination with a modified-live vaccine) show some protection against secondary challenge. While peripheral PRRSV-specific T cell responses have been examined, their direct contribution to antibody-mediated immunity and viral clearance have not been fully elucidated. The innate immune response following PRRSV infection, particularly the antiviral type I interferon response, is meager, but when provided exogenously, IFN-α enhances PRRSV immunity and viral control. Overall, the quality of immunity induced by natural PRRSV infection is not ideal for informing vaccine development programs.

The epitopes necessary for protection may be identified through natural exposure or modified-live vaccines and subsequently applied to vaccine delivery platforms to accelerate induction of protective immunity following vaccination. Collectively, further work to identify protective B and T cell epitopes and mechanisms by which PRRSV eludes innate immunity will enhance our ability to develop more effective methods to control and eliminate PRRS disease.

Published by Elsevier B.V.

Contents

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http://dx.doi.org/10.1016/j.vetimm.2015.07.003
0165-2427/Published by Elsevier B.V.

1. Introduction

PRRSV is a member of the Arteriviridae family, along with equine arteritis virus (EAV), lactate dehydrogenase elevating virus (LDV) of mice, and simian hemorrhagic fever virus (SHFV). The PRRSV genome is a positive-sense, single-stranded RNA of approximately 15 kb that encodes 10 open reading frames (ORF): ORF1a, ORF1b, ORF2a, ORF2b, and ORFs 3–7, which includes ORF5 and ORF5a (Firth et al., 2011; Johnson et al., 2011). ORF1 (a and b) code for two large polyproteins that are cleaved into 14 nonstructural proteins (Fang and Snijder, 2010). There are seven structural proteins encoded by ORF2a, ORF2b, ORF3-7 and ORF5a: glycoprotein (GP) 2, small envelope (E), GP3, GP4, GP5, membrane (M), nucleocapsid (N) proteins, and ORF5a protein (Dea et al., 2000; Meulenberg et al., 1995). GP5 and M can form a dimer, and GP2, GP3, and GP4 can form a hetero-trimer that has been shown to facilitate viral entry into the host cell (Mardassi et al., 1996; Wissink et al., 2005). PRRSV's are grouped into 2 genotypes; European (Type I) and North American (Type II) and there are significant genetic differences between the two genotypes. In addition, there is significant heterogeneity among strains within a genotype, giving rise to a significant number of antigenically distinct viruses, although a clear antigenic classification scheme has not been developed. Thus, protection against heterologous viruses with a vaccine is highly sought.

PRRSV infection is persistent, as numerous research studies have shown that virus can be isolated from lymphoid tissue months after the initial infection (Allende et al., 2000). However, the implementation of herd closure and farm stabilization protocols using exposure to wildtype PRRSV has shown that the virus can be eliminated from an individual animal and herd (Linhares et al., 2014; Torremorell et al., 2002). Therefore, the pig immune system is capable of mounting a response that eventually resolves the infection, eliminating the virus from the animal entirely. However, clearance and disease resolution takes a significant amount of time – most herd closure protocols indicate more than 200 days. Ultimately, this tells us that the pig eventually "sees" PRRSV in the context necessary to develop protective immunity and eliminate the virus from the body. This context most likely involves proper innate immune activation to adequately direct development of protective adaptive immunity. The portions of the virus that the immune system must target are eventually recognized and the immune cells necessary to mediate clearance are induced. Although it takes a long time for clearance, natural infection and subsequent convalescent immunity can be used to correlate specific immune parameters (T cell or antibody) to particular PRRSV epitopes that are involved in protection. While we can dissect this from immunity that develops post-exposure, the question remains, why does it take so long to get a protective immune response that can clear PRRSV infection?

The following review is focused on type 2 PRRSV and is structured based on the different arms of the immune response (antibody, cell-mediated, and innate) with the intent of outlining factors associated with protection or a lack thereof. It is well accepted that neutralizing antibody is a key component of sterilizing immunity (Osorio et al., 2002). For vaccine-based immunity, the rapid induction of neutralizing antibody is the ultimate goal, as it would provide protection against infection. Induction of antibody secretion from B cells requires T cell help, and T cells are required for killing virally infected cells; however, we know very little mechanistically about cell-mediated immunity against PRRSV. The final section relates to innate immunity, and is presented last because it aims to tie together findings described for adaptive immunity against PRRSV. As mentioned above, we know that pigs do eventually "see" PRRSV and can clear the infection. Thus, identifying the epitopes and immune cells necessary for clearance and pairing those antigens in the context of "proper" innate immune activation will be necessary to find solutions for enhancing PRRSV immunity, and developing strategies to significantly decrease the time it takes to develop protective immunity.

2. Antibody-mediated immune response to PRRSV

2.1. PRRSV-specific antibody response during infection

Early after PRRSV exposure a vigorous anti-PRRSV antibody response can be measured, with initial detection at 7–9 days post-infection (PI). However, there is no evidence that this early antibody response plays a role in the protection against PRRSV infection (Labarque et al., 2000; Yoon et al., 1994). The antibodies that appear during the early PI period do not neutralize PRRSV *in vitro* (Yoon et al., 1994) and when used in passive protection experiments, early PI antibodies (*i.e.* serum antibodies collected at 21 days PI) do not mediate passive protection against challenge with virulent antibody-matched PRRSV but rather seemingly enhance the virulence of the infection (Lopez et al., 2007). Serum antibodies with PRRSV-neutralizing activity appear only at later PI times, specifically at periods equal or higher than 28 days PI (Meier et al., 2000, 2003; Yoon et al., 1994).

The kinetics of antibody development, especially antibodies directed to the major structural proteins N, M and GP5 of PRRSV, has been studied in experimentally challenged pigs (Loemba et al., 1996; Nelson et al., 1994). PRRSV-specific IgM is detected at 7 days PI, with titers peaking between 14 and 21 days PI and decreasing to undetectable levels around 40 days PI. Anti-PRRSV IgG peaks at day 21 to 28 days PI, and levels remain elevated through the persistent phase of the infection. The earliest antibodies detected are directed against the 15 kDa N protein, followed by the 19 kDa M protein then the 26 kDa GP5 envelope glycoprotein (Loemba et al., 1996). Interestingly, NSP2 contains a cluster of non-neutralizing epitopes, suggesting an immunodominant role for this major nonstructural