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Novel PRRSV ORF5a protein is not immunoprotective but drives GP5 glycosylation

Sally R Robinson, Marina C Figueiredo, Juan E Abrahante, Michael P Murtaugh

Department of Veterinary and Biomedical Sciences, University of Minnesota, St. Paul, USA

Introduction

Porcine reproductive and respiratory syndrome virus (PRRSV) is an enveloped RNA virus responsible for PRRS in swine; a disease with significant animal welfare and economic implications for which there is no specific treatment and variable protection from vaccination due to viral genetic and antigenic diversity. Despite substantial knowledge of PRRSV biology, epidemiology, genome structure and complement of proteins, the precise mechanisms responsible for virulence, pathogenesis and protective immune response remain poorly understood. These factors limit progress towards designing effective measures for prevention and treatment of this devastating disease.

Recently, novel PRRSV ORF5a protein was identified, arising from an open reading frame (ORF) which overlaps the major envelope glycoprotein GP5 in a different reading frame[1,2]. The presence of ORF5a is evolutionarily conserved in all Arterivirus family members, is present in infected cells, is incorporated into virions, and elicits antibody production in pigs infected with PRRSV, indicating an important role in Arterivirus biology[2]. However, the function of ORF5a protein, whether it is critical to PRRSV infectious cycle or virulence, and its contribution to host immunity to PRRSV is unknown.

ORF5a Immunization

We hypothesized that ORF5a immunization would protect pigs against PRRSV challenge. Thus, pigs were immunized with a synthetic ORF5a peptide in adjuvant, and challenged with PRRSV VR2332. Immunized pigs had consistent serologic responses to ORF5a immunization. The antibody response was not immunodominant and antibodies did not neutralize virus. Robust antibody responses observed in some pigs did not translate to protection against viral challenge as evaluated by comparison of clinical response and PRRS viremia with control pigs.

ORF5a Conservation

PRRSV ORF5a protein has a highly conserved arginine-glutamine rich motif. Paradoxically, this conserved region arises from a region of nucleotide sequence that is dually responsible for the GP5 hypervariable region thought to be important for antigenic diversity in the alternate reading frame. To investigate how the nucleotide sequence could give rise to dual and opposing needs of ORF5a conservation and GP5 hypervariability, almost 5000 PRRSV sequences were analyzed to examine codon usage and selective pressures on this region. We found that purifying selection to maintain ORF5a protein drives GP5 variability through the effect of selective ORF5a codon usage on the GP5 reading frame. This also has implications for variation in GP5 glycosylation in this region where neutralizing epitopes have been described. We therefore propose that purifying selective pressure to maintain ORF5a protein rather than immunologic selection in GP5 determines hypervariability and glycosylation pattern in this region.

Summary

Presence of ORF5a protein across the Arteriviridae and the evolutionary pressure for ORF5a conservation suggests that it has important functional significance. It is therefore important to further understand the role of ORF5a protein, as this will enable greater insight to the molecular mechanisms of viral pathogenesis and host-pathogen interactions in order to design more effective prevention or treatment strategies for PRRSV.

References:

1. Firth AE, et al. Discovery of a small arterivirus gene that overlaps the GP5 coding sequence and is important for virus production. *J Gen Virol.* May 2011;92:1097-1106.

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