IDENTIFICATION OF DISEASE MECHANISMS AND CONTROL STRATEGIES FOR BVDV AT NADC

Shollie M. Falkenberg, MS, PhD | shollie.falkenberg@ars.usda.gov
Ruminant Disease and Immunology Research Unit, National Animal Disease Center,
USDA, Agricultural Research Service, Ames, IA, USA.

While all pestiviruses share the same genomic structure, heterogeneity is also a feature that is also common among all pestiviruses. This diversity in bovine pestiviruses can be observed in nucleotide sequences, antigenic properties, infections in difference host species, virulence, biotype, and different types of infections that include persistent and acute. Given the complexity of pestiviruses and the interactions with their hosts, it may seem difficult to find similar characteristics shared among bovine pestiviruses without over simplifying these interactions. While bovine pestiviruses share common aspects, it is still imperative to understand the uniqueness of each respective isolate and the spectrum that can still exist within each of the characteristics. For the purpose of this discussion, the characteristics that are shared among all pestiviruses to be further explored include; replication in immune tissues that leads to changes in immune cells and tissues, resulting in immunomodulation; the ability to cross the placenta; and antigenic cross-reactivity.

Previous research has described lymphopenia and thymic depletion associated with bovine viral diarrhea virus (BVDV) infections [6-8]. Further, it was determined that the degree of depletion was associated with the virulence of the virus [2]. The T cell population is of particular interest as the greatest decline is observed in the $CD4^+$ T-lymphocytes in the periphery, but this population returns to baseline values by day 14 after challenge with typical virulent BVDV isolates [2]. Additionally, significant depletion of the thymus is observed, which is the maturation site of T cells. Collectively this data causes concern as it relates to the long-term impact on the developing immune system as T cells contribute to cell mediated immunity and protective responses.

Modified-live vaccines are of particular interest, as only one killed vaccine has a fetal protection claim and previous research would suggest MLV vaccines confer greater fetal protection [15, 16]. While MLV vaccines may confer greater protection, this increased protection may come at a cost. As new vaccines are developed, an understanding of the impact vaccination has on the developing bovine immune system will be necessary to better compare the potential advantages and disadvantages of different vaccination strategies.

Furthermore, current licensed vaccines in the US only contain BVDV-1a and BVDV-2a strains [4], but the most recent surveillance would suggest that BVDV-1b strains are the most prevalent in the US [10-11]. This increased prevalence in BVDV1b isolates has been associated with lack of protection conferred by the current licensed vaccines. Protective responses associated with conferring fetal protection against BVDV involves several aspects of the immune response. Serum-neutralizing antibodies are an important component of the immune response. This is the most commonly used method, and considered the gold standard to evaluate protective responses against BVDV isolates that are genetically and antigenically diverse [1, 9]. While virus neutralization titers (VNT) are correlated with increased protection against BVDV [10, 15], other components of the immune response that may contribute to protection include mucosal immunity; cytotoxic T cells, which can kill virus infect cells; and T-helper-1 cells, which secrete IFN-γ and has anti-viral properties [11].

Other components of the immune response need to be considered and evaluated when describing protective responses. Serum virus-neutralizing antibodies may be sufficient to protect healthy non-stressed animals during an acute infection with BVDV, but conferring fetal protection may require a greater level of protection by effectively stimulating all aspects of acquired immunity [5], which needs to be measured in combination with neutralizing titers.

Previous research has highlighted the importance of cell associated BVDV by; demonstrating cows that give birth to PI animals have prolonged or increased viremia; the degree of viremia induced during BVDV infection is associated with clinical disease as defined by increased number of day of pyrexia and decrease in circulating lymphocytes; and PI calf health outcomes are associated with the frequency of BVDV positive PBMC populations [4, 14, 16]. Collectively, this research suggests that the frequency or amount of BVDV positive cells is an important indicator of clinical outcomes associated with BVDV infections and should be considered for immunological assays, but reliable and consistent methods for intracellular staining of BVDV by flow cytometry have been problematic [12, 13]. Only recently a new flow cytometry method was developed that reliably and reproducibly detects and quantifies the number of BVDV positive cells within respective cell populations at the single cell level [3, 4]. This new method of BVDV intracellular detection has been further expanded to evaluate competition between multiple BVDV isolates, as well as incorporate cell responses previously reported to be associated with CMI. Development of these new assays allows for a more comprehensive evaluation of protective responses as well as inherent difference that may exist between bovine pestiviruses.

Considering the collective immunological and serological data associated with both BVDV acute and persistent infections, significant evidence suggest that the T cell population plays a critical role in the outcome of BVDV infections. For this reason, this population of cells has been evaluated as it relates replication in immune tissues and lymphoid depletion; antigen specific responses in correlation with serological response, and it’s collective role in protective responses against fetal infections.

References

1. Alpay G, Yeşilbağ K (2015) Serological relationships among subgroups in bovine viral diarrhea virus genotype 1 (BVDV-1). Veterinary microbiology 175:1-6

2. Falkenberg S, Johnson C, Bauermann F, McGill J, Palmer M, Sacco R, Ridpath J (2014) Changes observed in the thymus and lymph nodes 14 days after exposure to BVDV field strains of enhanced or typical virulence in neonatal calves. Veterinary immunology and immunopathology 160:70-80

3. Falkenberg SM, Dassanayake RP, Neill JD, Ridpath JF (2017) Improved detection of bovine viral diarrhea virus in bovine lymphoid cell lines using PrimeFlow RNA assay. Virology 509:260-265

4. Falkenberg SM, Dassanayake RP, Walz P, Casas E, Neill JD, Ridpath JF (2019) Frequency of bovine viral diarrhea virus detected in subpopulations of peripheral blood mononuclear cells in persistently infected animals and health outcome. Veterinary immunology and immunopathology 207:46-52

5. Leyh RD, Fulton RW, Stegner JE, Goodyear MD, Witte SB, Taylor LP, Johnson BJ, Step DL, Ridpath JF, Holland BP (2011) Fetal protection in heifers vaccinated with a modified-live virus vaccine containing bovine viral diarrhea virus subtypes 1a and 2a and exposed during gestation to cattle persistently infected with bovine viral diarrhea virus subtype 1b. American journal of veterinary research 72:367-375

6. Liebler-Tenorio EM, Ridpath JF, Neill JD (2002) Distribution of viral antigen and development of lesions after experimental infection with highly virulent bovine viral diarrhea virus type 2 in calves. American journal of veterinary research 63:1575-1584

7. Liebler-Tenorio EM, Ridpath JF, Neill JD (2003) Distribution of viral antigen and development of lesions after experimental infection of calves with a BVDV 2 strain of low virulence. Journal of veterinary diagnostic investigation 15:221-232

8. Liebler-Tenorio EM, Ridpath JF, Neill JD (2004) Distribution of viral antigen and tissue lesions in persistent and acute infection with the homologous strain of noncytopathic bovine viral diarrhea virus. Journal of veterinary diagnostic investigation 16:388-396

9. Neill JD, Workman AM, Hesse R, Bai J, Porter EP, Meadors B, Anderson J, Bayles DO, Falkenberg SM (2019) Identification of BVDV2b and 2c subgenotypes in the United States: Genetic and antigenic characterization. Virology 528:19-29

10. Newcomer BW, Walz PH, Givens MD, Wilson AE (2015) Efficacy of bovine viral diarrhea virus vaccination to prevent reproductive disease: a meta-analysis. Theriogenology 83:360-365. e361

11. Platt R, Burdett W, Roth JA (2006) Induction of antigen-specific T-cell subset activation to bovine respiratory disease viruses by a modified-live virus vaccine. American journal of veterinary research 67:1179-1184

12. Qvist P, Aasted B, Bloch B, Meyling A, Rønsholt L, Houe H (1990) Flow cytometric detection of bovine viral diarrhea virus in peripheral blood leukocytes of persistently infected cattle. Canadian Journal of Veterinary Research 54:469

13. Qvist P, Houe H, Aasted B, Meyling A (1991) Comparison of flow cytometry and virus isolation in cell culture for identification of cattle persistently infected with bovine viral diarrhea virus. Journal of clinical microbiology 29:660-661

14. Walz PH, Bell TG, Wells JL, Grooms DL, Kaiser L, Maes RK, Baker JC (2001) Relationship between degree of viremia and disease manifestations in calves with experimentally induced bovine viral diarrhea virus infection. American journal of veterinary research 62:1095-1103

15. Walz PH, Givens MD, Rodning SP, Riddell KP, Brodersen BW, Scruggs D, Short T, Grotelueschen D (2017) Evaluation of reproductive protection against bovine viral diarrhea virus and bovine herpesvirus-1 afforded by annual revaccination with modified-live viral or combination modified-live/killed viral vaccines after primary vaccination with modified-live viral vaccine. Vaccine 35:1046-1054

16. Walz PH, Riddell KP, Newcomer BW, Neill JD, Falkenberg SM, Cortese VS, Scruggs DW, Short TH (2018) Comparison of reproductive protection against bovine viral diarrhea virus provided by multivalent viral vaccines containing inactivated fractions of bovine viral diarrhea virus 1 and 2. Vaccine