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The impact of BVDV infection on adaptive immunity

Christopher C.L. Chase*

Department of Veterinary and Biomedical Sciences, PO Box 2175, South Dakota State University, Brookings, SD 57007, USA

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ABSTRACT

Bovine viral diarrhea virus (BVDV) causes immunosuppression of the adaptive immune response. The level of suppression of the adaptive immune response is strain dependent. The early events of antigen presentation require activation of toll-like receptors that results in the release of pro-inflammatory cytokines. Non-cytopathic (ncp) BVDV infection stimulates cytokines from macrophages in vitro but the effect of BVDV infection in vivo on macrophages or in vitro with monocytes is not clear. Antigen presentation is decreased and co-stimulatory molecules are down regulated. T-lymphocytes numbers are reduced following BVDV infection in a strain dependent manner. There is recruitment of lymphocytes to the bronchial alveolar space following cytopathic (cp) BVDV infection. Depletion of T-lymphocytes occurs in the lymphoid tissue and is strain dependent. BVDV cp T-lymphocyte responses appear to be primarily a T helper 1 response while the response following ncp BVDV induces a T helper 2 response. Cytotoxic T-lymphocytes (CTL), an important BVDV defense mechanism are compromised. The major neutralizing antigens are well characterized but cross-protection between strains is variable. PI animals have normal adaptive immune responses with the exception of the PI strain immunotolerance and mucosal disease may be a function of the level of gamma delta T cells.

1. Introduction

Since the last reviews of adaptive immunity in BVDV in 2003 and 2004 [1,2], research has been aimed at all levels of the suppression effect of BVDV of the adaptive response from antigen presentation to B cell apoptosis. Additional work has been done since to understand molecular mechanisms along with in vivo studies that evaluated mucosal immunity in the lung and the intestinal tract. Studying BVDV interactions with the immune system is complicated by the nature of the infection (peracute, acute, or persistent), strain of virus (laboratory vs field strain, highly virulence vs low virulence) and the biotype [non-cytopathic (ncp) vs cytopathic (cp)]. Acute and peracute infections involve interactions with an intact immune system whereas persistent infected (PI) animals have an immune system with immunotolerance to BVDV that occurred during fetal development. Additionally, PI animals that develop mucosal disease (MD) have both the persistent ncp strain and the cp mutant that together (the pair) contribute to the development of MD. Since cp strains were the first BVDV viruses characterized, much of the important early bovine immune system work was done with acute infections with cp laboratory strains. Although this work laid the foundation for our understanding of the interaction with BVDV and the immune system, acute CP infections in the field are rare. Ncp strains are the predominate biotype of BVDV in the field and it is now clear that these ncp BVDV immune system interactions are quite different from CP BVDV strains. Ncp BVDV activates the humoral arm of the acquired immune system faster [3,4] and ncp BVDV traffics to more immune organs particularly those associated with mucosal immunity and BVDV antigen from ncp strains persists longer than cp in immune tissues [5]. In this review, the current knowledge of the BVDV adaptive response is summarized. The vast majority of the review details our understanding of BVDV acute infections but one section summarizes PI infections interactions.

2. BVDV and antigen presentation

2.1. Antigen presentation activation

Antigen presenting cells (APC) are pivotal for the induction and control of BVDV immune adaptive responses. However one of the greatest difficulties in understanding in vitro APC experiments is the type of APC cells infected with BVDV. The most potent APC of the monocyte-macrophage lineage are the dendritic cells (DC), followed by macrophages and then monocytes. APC first must be activated by danger signals through pathogen recognition receptors

* Corresponding author. Tel.:+1 6056885652; fax: +1 5046886003.
E-mail address: Christopher.Chase@sdstate.edu.

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(PRR) Fig. 1 [6]; Table 1 [7–9]. PRR include the membrane receptors, [toll-like receptors (TLR) and C-type lectin receptors (CLR)] and the cytoplasmic receptors [NOD-like receptors (NLR) and the RIG-1-like receptors (RLR)]. PRR are receptors present either on the surface or on cytoplasm of APC that bind to various molecules derived from microbes. These microbial ligands include lipopolysaccharide, peptidoglycans, cytosine guanine dinucleotide (CpG)-rich unmethylated oligonucleotides, and double stranded RNA (Table 1). PRR are the primary method for early detection and response to microbial invasion. Binding of microbial components to PRR initiates an inflammatory response that helps to activate other aspects of innate immunity and to initiate the acquired immune response (Table 1) including the production of pro-inflammatory cytokines, interleukin 1 beta (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) (Fig. 2; Table 2 [10,11]). Following binding of the microbial ligand by the cognate TLR, the pathogen is internalized, broken down into peptides that are then presented to T helper cells using major histocompatibility II molecules (MHC II) (Fig. 1). This "first signal", antigen recognition by the T cell, must then be followed by secondary signals (cytokines like IL-12 along with co-receptors such CD80/CD86) that are also induced by the PRR on the APC (Fig. 1).

2.2. BVDV, inflammation and pathogen-recognition receptor

The effect of BVDV infection on the antigen-presenting cell is dependent on the type of APC infected. Both monocytes and DC are susceptible to infection with ncp and cp BVDV and produce progeny virus [12]. However only monocytes are lysed by cp BVDV [12]. The first step of antigen presentation, activation, has only been studied in monocytes. TLR3 mRNA (ligand dsRNA-Table 1) was upregulated within 1-h post infection of monocytes with the NY-1 non-cytopathic (ncp) strain or NADL cytopathic (cp) strain but by 24 h post-infection the TLR-7 mRNA (ligand ssRNA-Table 1) response predominated [13]. There was an increase in pro-inflammatory cytokine tumor necrosis factor alpha (TNF-alpha) mRNA following infection with cp strain at 1 h post infection but by 24 h there was a decrease with either cp or ncp of the pro-inflammatory TNF-alpha or interleukin 1-beta (IL-1 beta) mRNA (Fig. 2) indicating a decrease in activation by 24 h [13].

2.3. BVDV, phagocytosis and antigen presentation

Phagocytic activity and the expression of major histocompatibility II (MHC II) on the surface of the APC are essential for the proper antigen presentation to T cells. The antigen must be phagocytized and digested into peptides that are then "presented" in the MHC II molecule (Fig. 1). BVDV infected APC have a reduction in Fc and C3 receptor expression, receptors that are required for phagocytic activity, which could be important for antigen uptake and presentation. The binding of Fc and/or C3 receptors activates a number of phagocytic activities so a reduction in receptors will decrease antigen uptake [14,15]. The effect of BVDV infection on antigen presentation also appears to depend on the virus strain and/or the maturity of the APC cells, with monocytes being the most effected and DC being the least affected [12]. In vitro infection of monocytes decreased the ability of monocytes to present antigen to T helper cells [12]. Proteomic analysis using cp strain 1a NADL or ncp strain 1b NY-1 indicated a decrease in MHC II with infection with the ncp strain NY-1 producing the largest decreases [16]. Peripheral blood mononuclear cells (PBMC) from cattle infected with the ncp type 2 BVDV field strain 24515 that resulted in high mortality and morbidity had reduced surface expression of MHC II [17] while MHC II expression on PBMC from cattle infected with ncp NY-1 was not affected [18,19]. Analysis of lymph node and Peyer's patch cells from BVDV-ncp NY-1 infected calves found a 30–50% decrease in the number of MHC II expressing cells [19]. Dendritic cells, the most important APC in the lymph node, were not affected

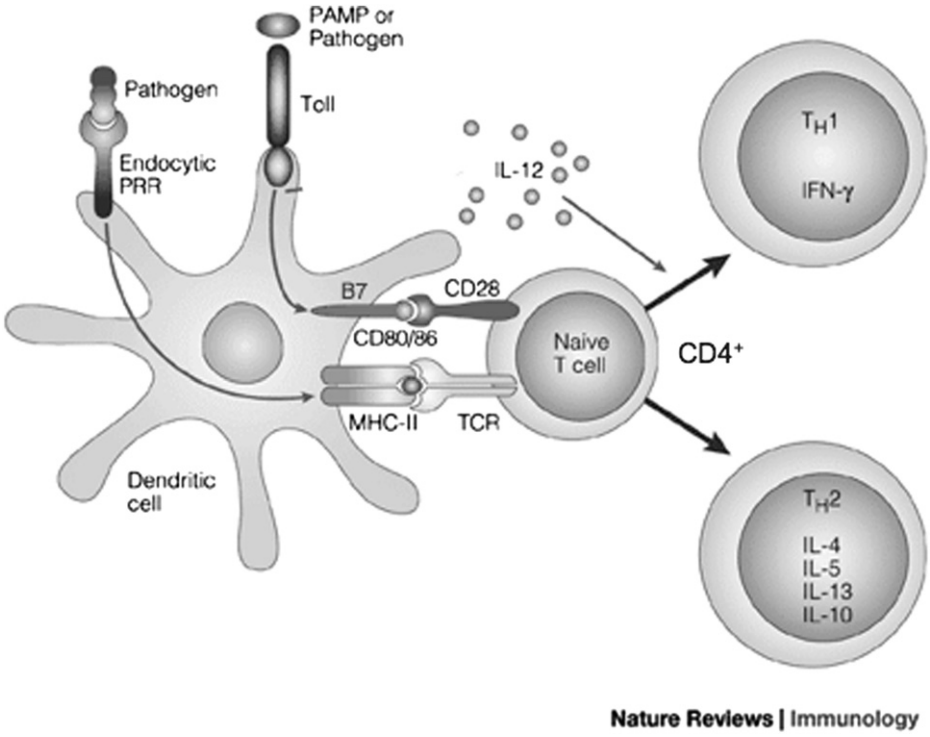

Fig. 1. Activation of antigen presenting cells and interactions with T cells. PRR = pathogen recognition receptor. PAMP = pathogen associated molecular pattern. Toll = toll-like receptor. B7/CD80/CD86 = APC co-receptor. CD28 = T cell co-receptor. MHC II = major histocompatibility II receptor expressed by APC that "presents" antigen to the T cell. TCR = T cell receptor. Adapted from Macmillan Publishers Ltd: NATURE REVIEWS IMMUNOLOGY Medzhitov R. Toll-like receptors and innate immunity, 1: 135–145, 2001.