New Paradigms for Bovine Viral Diarrhea Virus: Understanding How BVDV Interacts with the Immune System

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Introduction

Bovine viral diarrhea virus (BVDV) continues to be the bane of the US beef and dairy industry. BVDV infections cause clinical signs that vary from peracute death to inapparent infection. Even these inapparent BVDV infections can result in persistent infection (PI) of susceptible fetuses. The macrophage expresses cell surface markers that are important for phagocytosis and bacteria killing, and also for stimulation of T helper cells and for immune surveillance and killing by cytotoxic T cells (CTL). In this study, our objective was to measure the effect of BVDV on the macrophage function (phagocytosis and pathogen killing) and surface marker expression (CD14, MHCI and MHCII).

Materials and Methods

Bovine macrophages were developed from bovine monocytes and then infected with eight different strains of BVDV, six noncytopathic (NCP) and two cytopathic (CP). There were three type 1 and five type 2 viruses. The six noncytopathic strains were two highly virulent strains that cause severe acute (SA) disease, one strain that causes moderate disease and three strains that cause inapparent disease with high persistence (IDHP) in susceptible fetuses. Each of the strains was used to infect the macrophages and the following functional parameters were measured: phagocytic ability, microbicidal activity (fungal and bacteria) and NO production (microbicidal killing product). Surface marker expression for CD14 (receptor for gram negative bacteria), MHC I (receptor for CTL killing) and MHC II (receptor for T helper cells and antigen presentation) was measured using flow cytometry.

Results and Conclusions

Infection of macrophages with the highly virulent SA resulted in 50-60% decrease in phagocytosis by 24 hours. These viruses had a similar effect on the microbicidal activity against bacteria and fungi and also decreased NO production. On the other hand, the IDHP strains had no effect on phagocytosis or any of the other functions. Analysis of surface markers indicated that macrophages infected with SA strains had a 40-60% decrease in CD14 expression, while the IDHP strains had no effect on CD14 expression. MHC I expression was decreased 60-70% by the IDHP strains, and 30-40% by SA strains. CP virus increased MHC I expression. MHC II expression was decreased 60-70% by SA strains, 40-50% by CP, but IDHP strains did not inhibit MHC II expression.

What are the implications of this research? Taking the functional and CD14 results together, SA BVDV causes a decrease in the uptake and killing of gram-negative bacteria. The degree of inhibition correlates with the severity of clinical disease. One possible mechanism for the peracute deaths from BVDV may be that inhibition of the innate defense to kill gram-negative bacteria may result in unrestricted growth of the bacteria, resulting in endotoxic shock and death. The decreasing MHC I and II expression also affects pathogenesis, particularly PI. The most interesting aspect is that the clinical signs seen with the NCP viruses correlate directly their effect on macrophages. This research indicates that virulence is not related to genotype, and that different NCP BVDV isolates cause a wide spectrum of clinical disease that correlates with the effect on macrophages.