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Review Paper

Bovine leukemia virus: A major silent threat to proper immune responses in cattle

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ABSTRACT

Bovine leukemia virus (BLV) infection is widespread in the US dairy industry and the majority of producers do not actively try to manage or reduce BLV incidence within their herds. However, BLV is estimated to cost the dairy industry hundreds of millions of dollars annually and this is likely a conservative estimate. BLV is not thought to cause animal distress or serious pathology unless infection progresses to leukemia or lymphoma. However, a wealth of research supports the notion that BLV infection causes widespread abnormal immune function. BLV infection can impact cells of both the innate and adaptive immune system and alter proper functioning of uninfected cells. Despite strong evidence of abnormal immune signaling and functioning, little research has investigated the large-scale effects of BLV infection on host immunity and resistance to other infectious diseases. This review focuses on mechanisms of immune suppression associated with BLV infection, specifically aberrant signaling, proliferation and apoptosis, and the implications of switching from BLV latency to activation. In addition, this review will highlight underdeveloped areas of research relating to BLV infection and how it causes immune suppression.

Contents

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1. Introduction

Bovine leukemia virus (BLV) is a common infection in US dairy cattle and is the causative agent of enzootic bovine leukosis (EBL). EBL is characterized by three disease stages: asymptomatic or aleukemic (AL), persistent lymphocytosis (PL), and leukemia or lymphoma (Bartlett et al., 2013). Approximately 30% of infected animals will develop PL, while 0.1–10% of infected animals will develop either leukemia or lymphoma (Kabeya et al., 2001). Although BLV has been eradicated in 22 countries worldwide (Bartlett et al., 2014), BLV infection in the United States is widespread. Over 83% of US dairy herds are BLV-infected and the within-herd infection rates typically exceed 30% (USDA-NAHMS, 2007). A growing body of evidence supports that BLV infection negatively impacts dairy production in the US, which has recently been extensively reviewed (Bartlett et al., 2014). However, little is known about how BLV infection affects the risk of other infectious diseases in cattle, which could have a large impact on US dairy production.

Much research has been conducted on how BLV infection alters the host immune system. BLV preferentially infects B cells (Schwartz et al., 1994) and causes a benign, polyclonal expansion of B cells during PL (Meirom et al., 1997). However, evidence supports abnormal functioning of not only B cells, but also T cells and monocytes, including differential cytokine production, surface receptor expression and proliferative and apoptotic capacities. Despite evidence that BLV disrupts normal immune functioning, little research has investigated if this dysregulation impacts bovine immune health and increases the risk of developing other infectious diseases. Although a few studies have suggested that BLV infection increases susceptibility to other infectious diseases (Emanuelson et al., 1992; Erskine et al., 2011a; Trainin et al., 1996), it is essential to explore this risk more fully to best assess if and how the US should reduce BLV prevalence. This review will discuss research specific to the impact of BLV on immune cells and the immune system as a whole, as well as BLV latency and reactivation and how BLV's replicative strategy may impact immune health.

2. Abnormal immune function in BLV-infected cattle

2.1. Cytokine production and activity

One of the major effector functions of the immune system is production of cytokines, which have varied critical functions including the growth, polarization and responsiveness of various immune cell types and regulation of the strength and duration of immune responses. A large body of evidence indicates that BLV infection alters circulating cytokine levels and production of cytokines in response to stimuli. One study found that freshly isolated peripheral blood mononuclear cells (PBMCs) from PL cattle express less IL-2, IL-4 and IFNγ mRNA when compared to uninfected cattle, while fresh PBMCs from AL cattle express less IL-4 and IFNγ. PL cattle also express less IL-2 in comparison to AL cattle and possibly express less IL-10 as well (at $p < 0.1$) (Amills et al., 2002). Freshly isolated PBMCs from AL cattle have increased IL-12p40 mRNA in comparison to uninfected cattle, but PL cattle express less IL-12p40 mRNA in comparison to uninfected animals (Pyeon and Splitter, 1998). This reduction in cytokine gene expression in BLV-infected animals may indicate decreased cytokine transcription and, consequently, less cytokine activity in fresh PBMCs. Serum levels of IL-6 are also significantly higher in PL cows in comparison to serum from either AL or uninfected cattle (Trainin et al., 1996).

Immune cells from BLV-infected animals also demonstrate aberrant cytokine production in response to various stimulants *in vitro*. PBMCs isolated from PL cattle show increased IL-2 activity after culture with concanavalin A (ConA) compared to both AL and uninfected cattle (Sordillo et al., 1994). PBMCs from PL cattle cultured in the presence of either ConA, LPS, or BLV envelope protein gp51 also produce increased IL-6 in comparison to both AL and uninfected cattle (Trainin et al., 1996). ConA stimulation of cultured PBMCs isolated from PL and AL cattle also have increased IL-2, IL-10, and IFNγ expression when compared to uninfected cattle, although there is no difference in IL-4 production. In PBMCs from AL and PL cattle, IL-2 and IL-10 expression is delayed in culture, although IFNγ and IL-4 have the same expression kinetics as in cells from uninfected cattle (Trueblood et al., 1998). Although freshly isolated CD4+ lymphocytes from PL cattle produce less IL-2 and IL-4, IL-2 and IL-4 expression is similar between uninfected and PL cattle after culture in the presence of ConA (Amills et al., 2002). These *in vitro* results suggest that PBMCs from PL cattle are more sensitive to stimulation in culture than PBMCs from uninfected cattle.

The reported changes in *ex vivo* and *in vitro* cytokine expression are interesting because they cover a wide range of immune responses. IFNγ, IL-2 and IL-12 are all proinflammatory cytokines characteristic of a Th1 response (Mosmann et al., 1986), while IL-4 is characteristic of a Th2 or humoral response (Bao and Cao, 2014). IL-10 regulates and suppresses the proinflammatory immune response (Pestka et al., 2004). IL-6 can induce T cell activation and the development of B cells into plasmoblasts. Although there is no correlation between B cell leukemogenesis and IL-6