GENETIC FACTORS INFLUENCING SUBCLINCAL BOVINE LEUKEMIA VIRUS INFECTION

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Enzootic bovine leukosis (EBL) is a complex lymphoproliferative disease that has a significant impact on the dairy and beef cattle industries worldwide. The development of EBL is associated with chronic infection by the bovine leukemia virus (BLV). Some of the major features of the pathogenesis of BLV infection include: a) a variable period between the time of infection and seroconversion to the major viral envelope protein, BLV-gp51; b) proliferation of virus-infected B cells which results in a persistent B-cell lymphocytosis (PL) in approximately 1/3 of BLV-infected cattle; c) the appearance of antibodies to the viral core protein, p24, which is associated with the development of PL, and d) clinical lymphosarcoma, which develops in only 1 to 5% of BLV infected cattle.

We began to examine the role of the bovine major histocompatibility complex (known as BoLA) in EBL because of the well documented genetic components of susceptibility to development of PL and tumors. The BLV paradigm seemed to have great potential because of the high prevalence of BLV infection in most dairy herds (often greater than 70% seropositive) and because several subclinical stages of the disease could readily be identified (Lewin et al., 1988a). It has now been confirmed in at least three independent herds of Holstein-Friesian cattle that seroconversion to BLV-gp51 and progression to PL are BoLA-dependent. Cows with BoLA-w14 seroconvert at a significantly older age under natural conditions of exposure to the virus than do cows with other BoLA-A alleles. Cows with w14 (and w13) are also "resistant" to development of PL, whereas cows with BoLA-w12 seroconvert at a younger age and have a significantly higher incidence of PL and greater absolute numbers of B-cells in peripheral blood (Lewin et al., 1988b; Lewin, 1989).

Recent findings have demonstrated that expression of BoLA-DR (MHC class II) is dramatically reduced on B-cells from approximately 25% of cows with PL, whereas expression of class I and other class II products is not affected (Lewin et al., 1987). Also, the level of sIgM is greatly increased on PL B cells. Interestingly, tumor cells from all cases of lymphosarcoma that we have examined to date (N=5) have the same "low DR" phenotype. These findings suggest the possibility that loss of BoLA-DR is associated with progression of BLV infection from PL to tumors. It is possible that loss of BoLA-DR results in a failure of presentation of the immunologically relevant epitope necessary to control the proliferation of BLV infected B-cells.

Another interesting finding was that BoLA-DR can be induced by short term culture of B-cells from infected cows, under conditions which cause expression of the virus. However, BoLA-DR could not be "turned on" in tumor cells, which may be related to the presence of defective provirus in these cells. These findings are very similar to results observed for the IL-2 receptor in HTLV-I infected T-cells. Perhaps, as with HTLV-I, the *tat* protein, or other *trans*-acting factors of BLV, plays a role in regulating class II expression.

We have recently documented that high genetic potential for milk and for fat production are positively associated with the presence of antibodies to BLV-gp51 and the development of PL (Wu et al., 1989). Furthermore, cows with PL did not produce the amount of milk fat expected from their genetic potential. Milk fat percentage was also significantly lower in cows with PL (3.3±.09%) and other seropositive cows (3.48±.05%) compared with seronegative herdmates (3.67±.07%), suggesting a previously unrealized economic impact of subclinical BLV infection.

The dissection of the EBL paradigm will undoubtedly yield important information on the immunological and genetic features of retrovirus-induced and spontaneous neoplasms in outbred species. Clearly, subclinical progression of BLV infection is under the control of several genes. The combination of high levels of milk production and BoLA genotype appear to be the strongest influences on susceptibility to B cell lymphocytosis. Whether there are BoLA-linked genes that influence milk production and/or responses to physiological stressors remains to be determined. Elucidation of such pleiotropic effects of the BoLA system will be important for our overall understanding of the mechanisms of BoLA-linked resistance and susceptibility to infectious diseases.

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