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Bovine Leukaemia: Facts and Hypotheses Derived from the Study of an Infectious Cancer


INTRODUCTION

Bovine leukaemia virus (BLV) is the aetiological agent of a chronic lymphatic leukaemia/lymphoma in cows, sheep and goats. Infection without neoplastic transformation was also obtained in pigs, rhesus monkeys, chimpanzees, rabbits and observed in capybaras and water-buffaloes. Structurally and functionally, BLV is a relative of human T-lymphotropic viruses 1 and 2 (HTLV-I and HTLV-II). HTLV-I induces in humans a T-cell leukaemia and its type 2 counterpart has been found in dermatopathic lymphadenopathy, hairy T-cell leukaemia and prolymphocytic leukaemia cases. At variance with HTLV-I, BLV has not been associated with neurological diseases of the degenerative type.

BLV, HTLV-I and HTLV-II show clearcut sequence homologies. The pathology of the BLV-induced disease, most notably the absence of chronic viraemia, a long latency period and lack of preferred proviral integration sites in tumours, is similar to that of adult T-cell leukaemia/lymphoma induced by HTLV-I. The most striking feature of the three naturally transmitted leukaemia viruses is the X region located between the env gene and the long terminal repeat (LTR) sequence. The X region contains several overlapping long open reading frames. One of them, designated XBL-I, encodes a trans-activator function capable of increasing the level of gene expression directed by BLV-LTR and most probably involved in 'genetic instability' of BLV-infected cells of the B-cell lineage. The genetic instability puts the cell into a context of fragility, ready to move through a number of stages towards full malignancy. Little is known about these events and their causes; we present some theoretical possibilities.

BLV infection has a worldwide distribution. In temperate climates the virus spreads mostly via iatrogenic transfer of infected lymphocytes. In warm
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climates and in areas heavily populated by haematophagous insects, there are indications of insect-borne propagation of the virus.

BLV GENOME AND GENE PRODUCTS

Bovine leukaemia (lymphoma, lymphosarcoma) is a contagious disease induced by bovine leukaemia virus (BLV), a retrovirus exogenous to the bovine species. It is a chronic disease, evolving over extended periods (1–8 years), with tumours developing in only a small number of infected animals. The same virus infects sheep where it induces tumours with very high frequency.

The BLV proviral genomic structure (Figure 4.1) has been established in detail by several authors. Its salient features are:

1. The gag polyprotein contains virus structural proteins p15, p24 and p12;
2. A protease, p14, is coded by an open reading frame overlapping the gag gene on the left and the pol gene to the right; gag, protease (prot) and pol genes are in three different reading frames;
3. The env gene codes for a 72,000 env precursor (Pr 72env) that is cleaved into two glycosylated envelope proteins gp51 and gp30;
4. Two overlapping open reading frames, located between env and the 3’ LTR code for a 34 kDa and a 16 kDa protein, respectively.

Two gag polyprotein precursors, 66 kDa (70 kDa) and 44 kDa are synthesized in BLV-infected cells and in reticulocyte cell-free lysates, programmed with BLV 38 S RNA and in frog oocytes micro-injected with the same RNA message. The 66 kDa is the precursor to:

1. p15, myristilated fragment derived from the amino terminus;
2. p24, the major core protein;
3. p12, the RNA interacting fragment;
4. p14, the protease, probably synthesized via a frameshift suppression by a lysine-specific tRNA of the gag terminal codon.

The 44 kDa precursor lacks the p14 protease. P10 is an additional cleavage product found in purified BLV preparations; it is an amino terminal.