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How does Koala Retrovirus (KoRV) Induce Disease at the Genomic Level?

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Abstract. This manuscript summarizes the break-out session held on how does koala retrovirus (KoRV) induce disease at the genomic level at the *Koala Conservation Workshop: The koala and its retroviruses: implications for sustainability and survival* held at San Diego Zoo, April 17–18, 2013. The goals of this break-out session were to review current knowledge in this area and identify studies required to fill important gaps. KoRV is a gammaretrovirus with close similarity to MLV and FeLV, well-characterized pathogens of the laboratory mouse and the domestic cat. The parallel wth FeLV is particularly striking as cats harbor related endogenous retroviruses that share receptor specificity with endogenous KoRV. Also, transmission and pathogenesis of FeLV in its natural host is well understood and the virus is routinely controlled by measures that include vaccines. Alternative models for the roles of endogenous and exogenous KoRV in disease were discussed and prospective studies required to test these hypotheses were outlined.

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Introduction

What do we know? Most koala populations contain integrated KoRV-A. It appears that a subpopulation of koalas e.g. on Kangaroo Island (KI) may be free of KoRV, although available data based on PCR and hybridization analysis with KoRV-specific probes cannot be regarded as a definitive negative. The prevalence of disease appears to correlate with the copy number of KoRV, high in Queensland and low in other areas such as KI. Southern blot analysis of integrated KoRV from "high copy number" Queensland koalas reveals a similar pattern across tissues suggesting that most or all KoRV copies are germ-line rather than somatically acquired.

The length of time KoRV has been in the koala population is unclear but the recovery of integrated KoRV from koala skins in museum collections suggests that the infection may be older than previously supposed. However, the remarkably high copy number in some koala populations suggests that expansion of endogenous KoRV sequences may be more recent.

Analysis of lymphomas from captive koalas in US zoos has revealed the presence of variant KoRV with altered host range (KoRV-B, C) due to mutational changes in the viral *env* gene. They also show duplications of the core enhancer sequences in the viral LTR. Similar changes have been observed previously in murine and feline gammaretroviruses and are associated with increased replication in lymphoid tissues and leukemogenicity. These features suggest that KoRV induces lymphoma by an insertional mutagenesis mechanism similar to other gammaretroviruses. There is a further remarkable parallel between KoRV and feline leukemia virus (FeLV). Endogenous FeLV-related sequences, which are ancient (c. 6 million years) and invariably replication defective, encode an envelope protein that binds Pit-1, like KoRV-A. The prevalent infectious form of FeLV, FeLV-A, utilizes THTR1, like KoRV-B. FeLV-A recombines with endogenous FeLV to generate FeLV-B, and such recombinant viruses are more common in leukemic cats. However, the KoRV variants appear to arise by limited mutations from KoRV-A, presenting a challenge to the development of simple molecular typing and detection methods such as those used to analyse *de novo* integrated MLV and FeLV on a complex background of related endogenous viruses.