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Potential Role of Human Restriction Factors in Inhibiting the Emergence of Koala Retrovirus (KoRV) as a Zoonotic Agent

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Abstract. The findings of an exogenous koala retrovirus (KoRV) associated with neoplastic diseases in koalas *(Phascolarctos cinereus)* brought up the concerns of infection by koala retroviruses in humans, especially koala handlers. As simple retroviruses, koala retroviruses lack the regulatory genes to counter restriction activities by human restriction factors in viral replication. Koala retroviruses belong to gammaretroviruses. Previous studies of susceptibility of murine leukemia virus and a lab contaminant retrovirus, gammaretroviral xenotropic MLV-related virus, to human restriction factors disprove the possibility of gammaretrovirus as a human pathogen. There is no evidence that the koala retrovirus can infect and replicate in human peripheral blood mononuclear cells, which is consistent with the resistant role of human restriction factors against gammaretroviruses.

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Retroviruses have existed and co-evolved with eukaryotic cells for millions of years. According to the genome organization, retroviruses can be divided into two broad groups, "simple" and "complex" viruses. Simple retroviruses contain only *gag, pol,* and *env* genes. Gammaretroviruses, including murine leukemia virus (MLV), feline leukemia virus (FeLV), gibbon ape leukemia virus (GALV), and koala retrovirus (KoRV) are simple viruses. Complex viruses contain regulatory/accessory genes in addition to their functional genes. A well-known example of a complex retrovirus is human immunodeficiency virus-1 (HIV-1) that contains two regulatory and four accessory genes; the latter appear to be dedicated to evade host defenses.

Mammalian cells have developed various innate self-defense mechanisms during the long battle to defend against infection by retroviruses. Among these anti-viral mechanisms three major classes of human restriction factors that block or restrict retroviral replication at different stages of life cycle have been described in detail through the studies of ecotropic MLV and HIV-1, including the APOBEC3 family of DNA cytidine deaminases, tripartite motif protein 5-alpha (TRIM5α), and tetherin (Malim, 2009; Wolf & Goff, 2008).

Three potent human restriction factors

The APOBEC3 restriction system comprises a family of polynucleotide cytidine deaminases. APOBEC3 proteins can be efficiently packaged into retroviral particles and inhibit replication by deaminating cytosine residues converting them to uracil during the first step of reverse transcription-the synthesis of minus strand DNA, which in turn, results in the guanine to adenine transition mutations in plus strand

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