Technical Reports of the Australian Museum, Online (2014) No. 24, pp. 11–14.
ISSN 1835-4211 (online)
http://dx.doi.org/10.3853/j.1835-4211.24.2014.1607

Koala Retrovirus (KoRV): Molecular Biology and Evolution

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Abstract. The koala retrovirus (KoRV) is in transition between occurring as an exogenous retrovirus spread by infection and becoming an endogenous retrovirus spread primarily as part of the host germ line. While up to 10% of mammalian genomes are composed of such endogenous retroviruses (ERVs), KoRV is the only known example of a retrovirus in the process of making this transition. Thus, it presents a singular opportunity to study the host-pathogen interactions involved during retroviral invasion of a vertebrate germ line.

Greenwood, Alex D., and Alfred L. Roca. 2014. Koala retrovirus (KoRV): molecular biology and evolution. In *The Koala and its Retroviruses: Implications for Sustainability and Survival*, ed. Geoffrey W. Pye, Rebecca N. Johnson and Alex D. Greenwood. *Technical Reports of the Australian Museum, Online* 24: 11–14.

Overview of KoRV molecular biology

KoRV is most similar genetically to the gibbon ape leukemia virus (GALV). However, biologically, they are quite different. GALV is a highly aggressive oncogenic virus whereas KoRV, while associated with leukemia in koalas, is not as infectious (Hanger *et al*., 2000). Molecular studies of the genetic differences between KoRV and GALV have demonstrated that specific mutations likely account for the decreased pathogenicity of KoRV relative to GALV (Oliveira *et al*., 2006, Oliveira et al., 2007). Thus, replacing important GALV domains with their KoRV homologues decreases the infectivity of the GALV recombinants. Recently, however, an infectious KoRV clone has been developed that, despite its molecular differences with GALV, remains quite capable of infecting and replicating in tissue cultures from many mammalian species (Shojima *et al*., 2013). This KoRV clone provides a novel resource for comparative studies. Since this KoRV clone can infect a wide variety of mammalian cell types, it is not clear why KoRV has only been detected in koalas and is not more widely distributed.

KoRV titres are positively correlated with infection by the bacterial pathogen *Chlamydia*, which has a severe impact on koala health (Tarlinton *et al*., 2008). The interaction between KoRV and *Chlamydia* in terms of koala health needs to be clarified, in order to design appropriate interventions. Currently, research on KoRV and *Chlamydia* occur largely independently of one another, although both would benefit from coordination of efforts.

Genomically, KoRV integration sites vary across infected individuals, most likely KoRV inserts largely at random across the genome of koalas (Hanger *et al*., 2000; Tarlinton *et al*., 2006). In northern Australian koala populations, some copies of KoRV are found at the same locus across individuals, suggesting that the virus has been vertically transmitted as an endogenous retrovirus, i.e., has become part of the germ line. The KoRV genome is highly but variably expressed in tissues of infected individuals, as is common for exogenous and endogenous retroviruses alike (Seifarth *et al*., 2005). Among various other ERVs, expression of endogenous proviruses may evolve to benefit the host species, e.g., through development of novel gene

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