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The Role of Koala Retrovirus Integrations in Promoting Neoplasia in Koalas (*Phascolarctos cinereus*)

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Abstract. Koalas suffer unusually high rates of neoplasia. There has been a long-standing correlation between koalas with the koala retrovirus (KoRV) and development of neoplasia which has lacked a mechanistic explanation. We describe recent results that demonstrate that many KoRV integrations lead to neoplasia by (*I*) inserting into somatic cells preferentially near oncogenes, (*II*) inserting into germ cells near oncogenes predisposing koalas to cancer, and (*III*) transduction—replacing KoRV genes with oncogenes, resulting in drastic upregulation of the transduced gene. The high mortality associated with integration-driven promotion of neoplasia may explain the increased prevalence of dysfunctional recombinant KoRVs (recKoRVs), which, over time, could replace KoRV, thereby slowing the production of novel detrimental integration sites.

Introduction

Koalas develop neoplasia at rates at least an order of magnitude higher than humans and many other mammals (Gonzalez-Astudillo *et al.*, 2019). Approximately 3% of wild koalas from southeast Queensland brought into veterinary clinics had lymphoma and 7% had lymphoid neoplasms (Gonzalez-Astudillo *et al.*, 2019; Fabijan *et al.*, 2020). This is likely an underrepresentation as it is unlikely that wild koalas manifesting late stage leukaemia or lymphoma will be found when they die. In contrast, in zoos where observation of koalas is continuous, 25% developed lymphoma (Gillett, 2014). This tremendous cancer burden has been associated correlatively with koala retrovirus (KoRV) infection, either as a quantitative increase of KoRV expression in koalas suffering from neoplasms or as an increase in the number of variants of KoRV expressed (Tarlinton *et al.*, 2005; Quigley *et al.*, 2019). A causative relationship and mechanistic explanation for the elevated cancer risks faced by koalas with KoRV has not been provided until now.

In general, there are four major mechanisms by which KoRV as a gammaretrovirus could cause cancer in koalas: I. insertional mutagenesis in somatic cells, II. non-lethal insertional mutagenesis in the germline in or near genes that promote the development of cancer later in life, III. transduction of oncogenes whereby the retrovirus incorporates an oncogene sequence in its genome and expresses it above the normal host rate, and IV. immune suppression by expression of the immunosuppressive domain in the envelope protein preventing host immune cell recognition and clearing of cancerous cells. We have recently provided evidence supporting a role for I-III (McEwen *et al.*, 2021). Ten paired tumour and neoplastic tissues were obtained from koalas from Queensland, Australia. Seven of the animals died or were euthanized because of advanced lymphoma. Three animals, all from one population, died of osteosarcoma. The integration site (IS) profile for each tissue sample and assorted positive and negative controls was determined using a novel long inverse PCR approach followed by large fragment high throughput sequencing

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