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Koala Immunology and the Koala Retrovirus (KoRV)

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Abstract. Although koala retrovirus (KoRV) is widely termed a pathogen, direct evidence for causation of disease impacts in koalas *(Phascolarctos cinereus)* remains elusive. Examination of the immune system of koalas could provide a sharper tool to investigate this but progress has been slow due to a paucity of immunological reagents in this species, and historical contradictions in research findings in this area. Our work using cross reactive antibodies to examine behaviour of resting and stimulated koala T cells (anti-human CD3); B cells (anti-human CD79b); MHCII (anti-human HLA-DP, DQ, DR) and interferon gamma (anti-bovine IFNg) by flow cytometry have revealed some features consistent with a skew to a Th2 (B cell) immune focus. Assessing the role of KoRV in immunomodulation in koalas clearly requires more in-depth research. We have used recent advances in genomics of other marsupials to develop tools necessary to assess KoRV's effects on koala immune function in free-ranging, captive and in-vitro systems.

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Immunosuppression in koalas: is it clear-cut?

Early researchers working on koala immunology formed the belief that koalas were immunologically "lazy", and this has coloured perceptions of koala immunology in the broader community ever since. This idea was originally put forward based on apparently slow seroconversion to chlamydial infection, and a limited cellular response to overwhelming sarcoptic mange in a small number of koalas (Brown, 1988). It sparked a series of studies that pioneered marsupial immunology but also set the scene for two decades of intriguingly disparate findings: lymphoid tissues of koalas are generally more sparsely populated than those of many species (Wilkinson *et al*., 1992a), yet the arrangement of these tissues is consistent with those of eutheria, with similar distribution of T and B cells (Hemsley *et al.,* 1995, 1996a, b); initial experiments indicated slow and weak local cutaneous delayed type hypersensitivity reactions (Wilkinson *et al*., 1994), yet koalas are clearly capable of mounting prolific lymphoplasmacytic responses, with their inflammatory infiltrates and distribution of B and T lymphocytes in chlamydial disease being very similar to the non-protective, deleterious response to conserved chlamydial heat shock proteins that induces pelvic inflammatory disease in humans (Hemsley & Canfield, 1997; Morrison, 1991). Similarly, in contrast to poor antibody responses described initially (Wilkinson *et al*., 1992b; Wilkinson *et al*., 1994), recent vaccine trials induced strong humoral and cellular responses (Carey *et al*., 2010; Kollipara *et al*., 2012). Also, in response to natural *Chlamydia pecorum* infection, koalas develop neutralizing anti-MOMP antibodies (Girges *et al*., 1993), and also develop high anti-hsp60 and hsp10 antibody titres in association with chlamydial reproductive tract fibrosis (Higgins *et al*., 2005), as do women similarly affected by *C. trachomatis* (Domeika *et al*., 1998; LaVerda *et al*., 2000).

Clearly, we have evidence of outcomes of a functional adaptive immune response in the koala. However, in terms of its strengths and weaknesses, and the evolutionary forces that have shaped it, we are just beginning to scrape the surface. KoRV as a potential immunosuppressive agent needs to be considered in the context of a range of forces

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