"Friendly viruses": antiviral activities of ERVs against the oncogenic Jaagsiekte sheep retrovirus.

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Endogenous retroviruses (ERVs) originate from ancient retroviral infections of the germ line and are transmitted vertically from generation to generation. Nowadays, the majority of ERVs are defective; however some of them have maintained part or all of their genes intact for millions of years, suggesting that they have provided a beneficial role to their host. We have studied the complex interplay between ERVs, exogenous pathogenic retroviruses and their host using sheep as model system. Jaagsiekte sheep retrovirus (JSRV) is the causative agent of ovine pulmonary adenocarcinoma and coexists with highly related endogenous retroviruses (enJSRVs) that colonized the sheep genome throughout evolution. Interestingly, we discovered that enJSRVs play a critical role in conceptus development and placental morphogenesis of sheep. In addition, *in vitro,* these enJSRVs are able to block JSRV at early and late steps of the retroviral cycle. Indeed, JSRV and enJSRVs use the same cellular receptor (Hyaluronidase 2) and enJSRVs envelope proteins can prevent JSRV entry by receptor competition. Moreover, two enJSRV proviruses (enJS56A1 and enJSRV-20), which entered the host genome within the last 3 million y, acquired in two temporally distinct events a defective Gag polyprotein resulting in a transdominant phenotype able to block late replication steps of related exogenous retroviruses. These two "protective" proviruses became fixed in the genome of domestic sheep supporting the idea of their positive selection during, or immediately before, sheep domestication (9,000 years ago). Interestingly, we also identified a recent provirus (< 200 years old) with an intact genomic organization that escapes the restriction induced by enJS56A1 and enJSRV-20. These data provide evidence that the invasion of the sheep genome by endogenous retroviruses is still ongoing and has not reached an equilibrium yet. Therefore, sheep provide an exciting model to study the co-evolution between ERVs and their host.

Keywords: virus–host co-evolution, ovine pulmonary adenocarcinoma, endogenous retroviruses and viral restriction.