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Paleovirology of human endogenous retroviruses

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Retroviral infection usually occurs within somatic cells, but occasional infection of germ line cells can lead to integrated retroviral genomes being vertically inherited as host alleles called endogenous retroviruses (ERVs). Once within the host germ line, retroviral genetic material can proliferate via a variety of mechanisms, giving rise to multi-copy 'families' of ERV sequences. ERVs serve as a kind of molecular 'fossil record' for the various forms of retroviruses that have that circulated throughout the Cenozoic Era. However, most ERV families are comprised entirely of sequences that have accumulated numerous mutations, deletions, and insertions. The use of ERVs to explore the biology of the ancient infectious retroviruses requires methods for 'paleovirological' reconstruction of ancestral retroviral genomes using highly mutated ERV sequences. For accurate reconstructions, methods must account not only for mutational changes that have occurred due to genetic drift during host DNA replication, but also for a range of additional factors that can influence the evolution of ERV sequences. These include; (i) host-mediated editing of retroviral sequences, (ii) methylation of CpG dinucleotides, and (iii) selection pressures that vary depending on the mechanism of ERV proliferation and the biological consequence of ERV expression in the host species. We describe a systematic approach to using ERV insertions for paleovirological reconstruction of ancestral, infectious retrovirus genome sequences. We use this approach to reconstruct ancestral genome sequences for 15 major human ERV (HERV) lineages. Using these reconstructed ancestral sequences, we re-evaluate the evolutionary relationships of HERVs and modern exogenous retroviruses, and estimate the time-period over which the exogenous viruses from which these 15 HERV lineages are derived are likely to have circulated amongst mammalian species.