

12 months in subtype B and KSB patients, respectively ($P < 0.001$). In contrast, KRG treatment did not affect the $g\Delta nef$ in non-B. However, the proportion of sequences with premature stop codon was similar among 3 subtypes (0.5–2.0 %). Sequence identity over 6 years was significantly higher in KSB (97.8 ± 1.1 %) than subtype B (96.1 ± 1.6 %) ($P < 0.01$) and non-B (96.8 ± 1.5 %) ($P < 0.01$). The sequence identity 97.8 ± 1.1 % was also higher than 96.4 ± 2.0 % in KSB control ($P < 0.01$). Taken collectively, 23 long-term slow progressors (LTSPs) was detected in KRG treated patients only ($P < 0.01$) and its proportion was higher in KSB patients than in non-B patients ($P < 0.01$).

Conclusions: Decrease of CD4 and proportion of $g\Delta nef$ are affected by subtypes and KRG treatment. Faster decrease of CD4 in non-B patients than in KSB patients is supported by significantly lower $g\Delta nef$ and higher variation in non-B than KSB.

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Aberrant expression of ERVWE1 endogenous retrovirus and overexpression of TET dioxygenases are characteristic features of seminoma

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Background: Germ cell tumors and particularly seminomas reflect the epigenomic features of their parental primordial germ cells, including the genomic DNA hypomethylation and expression of pluripotent cell markers. Because the DNA hypomethylation might be a result of TET dioxygenase activity, we examined expression of TET1–3 enzymes and the level of their product, 5-hydroxymethylcytosine, in a panel of histologically characterised seminomas and non-seminomatous germ cell tumors. Simultaneously, we analysed the expression of ERVWE1 endogenous retrovirus whose spliced form codes for envelope glycoprotein called Syncytin-1. Syncytin-1 has fusogenic ability and its expression is restricted to placenta under physiologic conditions.

Results: We found highly increased expression of TET1 dioxygenase in most seminomas and a strong TET1 staining in seminoma cells. Isocitrate dehydrogenase 1 and 2 mutations were not detected suggesting the enzymatic activity of TET1. The levels of 5-methylcytosine and 5-hydroxymethylcytosine in seminomas were found decreased in comparison to non-seminomatous germ cell tumors and healthy testicular tissue. Seminomas further displayed significant increase in both spliced and non-spliced forms of ERVWE1 in comparison to healthy controls. Importantly, the promoter of ERVWE1 in seminomas contained low levels of DNA methylation.

Conclusions: We propose TET1 expression as a marker of seminoma and mixed germ cell tumor. Furthermore, the endogenous retrovirus ERVWE1 was consistently overexpressed in seminomas. In contrast to the CpG island methylator phenotype observed in a fraction of tumors of various types, we suggest the anti-methylator phenotype in seminomas is maintained by TET1 demethylation activity.

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Life history of the oldest lentivirus: characterisation of ELVgv integrations and the TRIM5 selection pattern in dermoptera

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Endogenous retroviruses are genomic elements formed by germline infiltration by originally exogenous viruses. These molecular fossils

provide valuable information about the evolution of the retroviral family. Lentiviruses are an extensively studied genus of retroviruses infecting a broad range of mammals. Despite a wealth of information on their modern evolution, little is known about their origins. This is partially due to the scarcity of their endogenous forms. Recently, an endogenous lentivirus, ELVgv, was discovered in the genome of the Malayan colugo (order Dermoptera). This represents the oldest lentiviral evidence available and promises to lead to further insights into the history of this genus.

In this study, we analysed ELVgv integrations at several genomic locations in four distinct colugo specimens covering all the extant dermopteran species. We confirmed ELVgv integrations in all the specimens examined, which implies that the virus originated before the dermopteran diversification. Using a locus-specific dermopteran substitution rate, we estimated that the proviral integrations occurred 21–40 million years ago. Using phylogenetic analysis, we estimated that ELVgv invaded an ancestor of today's *Dermoptera* more than 60 million years ago. We also provide evidence of selective pressure on the *TRIM5* antiviral restriction factor, something usually taken as indirect evidence of past retroviral infection. Interestingly, we show that *TRIM5* was under strong positive selection only in the common dermopteran ancestor and that this period could coincide with ELVgv activity. In summary, we describe the evolutionary history of the oldest known lentiviral lineage and propose its coevolution with the *TRIM5* host restriction factor.

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Characterisation of a highly divergent endogenous retrovirus in the equine germ line

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The general profile of endogenous retroviruses (ERVs) in the domestic horse (*Equus caballus*) genome has been described, but a thorough characterisation is lacking. We used an in silico approach based on data mining and phylogenetic analysis to profile equine ERVs in depth. We identified a total of 1384 ERV loci in the horse genome that disclosed a robust phylogenetic relationship to retroviral reverse transcriptase (RT) genes. Through phylogenetic and genomic analyses of these loci we derived an overview of equine ERV diversity. We inferred that there are at least 8 distinct, major lineages of ERVs in the equine germ line, and recovered consensus proviral genome structures for each of these. One highly divergent ERV lineage, which we provisionally refer to as 'EqERV-u1', was observed to be unique to the family *Equidae*. We show that EqERV-u1 is intermediate to Alpha- and Betaretroviruses in phylogenetic trees, and identify 46 distinct EqERV-u1 proviruses, including 17 with intact genomes. Interestingly, we observed two distinct genome structures among intact EqERV-u1 copies: a classical (type I) structure in which a *dUTPase* gene is located between the *pro* and *pol* coding domains, and a type II structure—unique to EqERV-u1—in which a *dUTPase* gene occurs upstream of *gag*. We dated the activity of the EqERV-u1 lineage over time using a molecular clock-based approach, revealing that it has been active relatively recently (i.e. within the past 1–5 million years), even though it may have entered the equid germline >18 million years ago. Analysis of published *E.cabalu*s transcriptome data revealed that one EqERV-u1 provirus on chromosome 29 is actively transcribed in a tissue-specific manner. This provirus exhibits the unusual type II genome structure.

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The emergence of pandemic retroviral infection in small ruminants

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During the 20th century a confluence of socio-epidemiological factors combined to facilitate the emergence of retroviral pathogens in humans. However, the influence of anthropogenic factors on the emergence of retroviral infections in non-human species has not been evaluated to the same extent. Small ruminant lentiviruses (SRLVs) cause chronic, persistent infections in populations of domestic sheep (*Ovis aries*) and goats (*Capra hircus*) throughout the world. Here, we trace the origins and history the SRLV pandemic. To investigate the ancient history of SRLVs, we performed a serology and DNA sequencing-based investigation of SRLVs diversity in the Fertile Crescent region, where domestication of sheep and goats is thought to have originally occurred. Screening of 886 sheep and goats in Jordan and Lebanon revealed a relatively high prevalence of infection (~21 %) and an elevated level of viral genetic diversity compared to other regions of the world. Furthermore, using sequences obtained via this screen, we show that currently circulating SRLV genotypes reveal evidence of ancient, inter-genotype recombination. These data support the hypothesis that SRLVs disseminated out of Western Asia during the early Neolithic period. However, by using phylogenetic and phylogeographic approaches to analyze SRLV sequences sampled from 600 distinct infections in 30 different countries, and spanning a period of 64 years, we show that pandemic spread of SRLVs did not occur until the 20th century. We integrate the findings of our analysis with historical and epidemiological evidence to propose a geographic sequence and timeline for the emergence of the SRLV pandemic. We identify the Colonial expansion of European nations during the 'Age of Imperialism' (~1870–1950), and the associated development of novel agricultural systems, as having played a key role in enabling the global spread of SRLV infection.

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Near full-length genome (NFLG) characterisation of HIV-1 subtype B identified in South Africa

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Background: The first reported cases of HIV-1 infection in South Africa occurred in 1982, which was initially spread by MSM. Almost 7 million people are living with HIV-1 infection in South Africa and 2 separate epidemics have been described. The majority of these infections are caused by HIV-1 subtype C, spread through heterosexual contact. The minor subtype B epidemic in South Africa was, in the past, transmitted via MSM. We recently described the detection of new BC URFs circulating in the country. This indicates that both epidemics are still co-circulating in South Africa, but only 6 HIV-1 subtype B NFLGs sequences have been previously characterised.

Methods: Ten samples were selected for NFLG amplification. Seven of the samples were obtained from the late 1980s, while the other three samples were from more recent infections. The NFLG amplification was performed using a PCR protocol designed to target two overlapping 5.5 kb fragments. There after samples were sequenced through conventional "Sanger" sequencing and next-generation sequencing (NGS) using the Illumina MiSeq platform. The samples were subtyped using the REGA, COMET, RIP and jPHMM online tools. Multiple sequence alignments were done using MAFFT and then codon aligned. Maximum likelihood phylogenetic trees were constructed in Geneious 9 and MEGA.

Results: The six 1980s samples were obtained from MSM in the Western Cape South Africa. The others obtained were from a 16 year old heterosexual teenager in Gauteng, one woman from the Eastern Cape and one woman from the Western Cape. Two of the subtype B NFLG sequences obtained cluster with reference subtype B strains from the 1980s. Three sequences cluster more closely with reference strains from the late 1990s. Another sequence was identified as a unique BC recombinant strain.

Discussion: We have detected and characterised HIV-1 subtype B strains circulating in South Africa since the early 1980s to 2000s. This

subtype B epidemic crossed over into the heterosexual population, as indicated by infection of both children and women in the different provinces of South Africa of concern is the characterisation of the newly described subtype BC URF strains. We will continue to monitor the HIV-1 subtype B epidemic in the heterosexual population in South Africa.

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Acquisition of Vpu-mediated tetherin antagonism by an HIV-1 group O strain

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The restriction factor tetherin inhibits the release of enveloped viruses and imposes a barrier for efficient spread of HIV in the human population. The direct precursors of HIV-1, SIVcpz and SIVgor, use their Nef protein to antagonize the tetherin orthologue of their respective hosts. Because of a five amino acid deletion in its cytoplasmic tail, human tetherin is resistant to SIV Nef. Overcoming this hurdle may have been a prerequisite for effective spread of HIV-1 in humans. Pandemic HIV-1 group M strains acquired Vpu-mediated anti-tetherin activity during human adaptation to overcome this hurdle. In contrast, HIV-1 group O Vpus do usually not counteract human tetherin. Instead, the accessory Nef protein of group O viruses evolved the ability to target a region adjacent to the deletion to antagonize tetherin in humans. Here, we demonstrate that the infectious molecular clone of HIV-1 O RBF206 utilizes both Nef and Vpu to antagonize human tetherin. Using FACS analyses and virus release assays, we show that the RBF206 Vpu is as efficient as the group M NL4-3 Vpu in reducing cell surface levels of human tetherin and promoting virus release. Unlike that of NL4-3, the RBF206 Vpu also efficiently antagonizes the second shorter isoform of human tetherin that lack the first 12 amino acids. In the NL4-3 context, both Nef and Vpu reduce cell surface levels of human tetherin in infected PBMCs and promote virus release in 293T cells. Our data suggest that HIV-1 group O is still adapting to human tetherin and further illustrate the enormous capacity and plasticity of Vpu and Nef proteins in counteracting cellular defense mechanisms.

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The human endogenous retrovirus type K is involved in cancer stem cell markers expression and in human melanoma malignancy

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Increasingly scientific evidence underline retroelements and in particular human endogenous retroviruses (HERVs) as important players in cell plasticity, transformation and tumour progression. Expression of the HERV-K, especially the HML-2 family, was found elevated in melanoma and has been suggested to be implicated in the etiopathogenesis of the disease. We previously demonstrated that HERV-K activation and viral particles production were associated to aggressiveness and immune evasion of metastatic melanoma cells. However, melanoma consists of heterogeneous cell populations whose biological