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Endogenous retroviruses – Aiding and abetting genomic plasticity

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Introduction (Part of a Multi-author Review)

Retroviruses cause disease by infecting cells, injecting their viral single-stranded RNA genome into them and then using their own RNA-directed DNA polymerase to make a double-stranded DNA copy of the viral genome. Integration of this retroviral DNA into the genome of the infected host cell allows the virus to use the host cell's DNA-directed RNA polymerase to make messenger RNA and subsequently viral proteins. Making use of the host cell machinery, viral genomic RNA is packaged and exported from the cell. This process engenders a new generation of virus particles competent to infect neighboring cells or organisms. Retroviruses that maintain their existence by moving from cell to cell, and organism to organism via serial infection events are called exogenous retroviruses. Occasionally, exogenous retroviruses gain the ability to infect germ cells. If this happens, a profound shift in the history of the retrovirus can occur. If germ line-integrated provirus gains a foothold within the species of the infected individual through vertical transmission to its offspring, an endogenous retrovirus comes into existence. This has happened often within mammalian and proto-mammalian species. In fact, retroviral endogenization is so frequent and ancient an occurrence that fragments of viruses, collectively called endogenous retroviruses or ERVs, have been used to distinguish inheritor species from one another as they and their accreted ERVs evolve.

ERVs are present in the genomes of birds, reptiles, amphibians, fish and mammals. Over millions of years, most retroviral genomes and retroelements residing in their host DNAs have been rendered inactive or suppressed by epigenetic mechanisms or mutations. Thus, an understanding of the initial process of how retroviruses enter their host genomes has not been scientifically feasible. This changed recently and dramatically with the discovery of a pathogenic retrovirus that entered the germ line of koalas within the last 200 years [1, 2]. Endogenizing koala retrovirus (KoRV) has retained its ability to produce infectious virus [3]. KoRV is most closely related to gibbon ape leukemia virus (GALV), which was first identified in the early 1970 s as an exogenous retrovirus associated with lymphosarcoma and myeloid leukemia in captive gibbons [4]. The adaptive process by which an infectious, leukemogenic ERV becomes a domesticated form of itself, tolerated as a permanent resident in its host, can now be investigated by comparing changes that distinguish KoRV from its exogenous counterpart, GALV. Changes in KoRV proteins that attenuate its virulence and affect its unique host range properties have already been identified [5, 6].

The outcomes of maintaining infectious ERVs or functional ERV elements are variable, and they profoundly influence the evolution of the host genome. ERVs may play a role in speciation or provide the opportunity for the evolution of a fitter species. Animals such as koalas and mice that harbor intact ERVs serve as virus reservoirs, which promote intra-species and interspecies transmission of ERVs. Many fully functional ERVs, although not expressed in their hosts, can be activated by a variety of agents or by tissue explantation, with porcine endogenous viruses (PERVs) as a prime example [7]. Xenotransplantation of porcine tissue presents the inherent risk of the transfer of PERVs that can infect human recipients, illustrating how replication-competent ERVs can pose a threat with regard to interspecies infections. ERV components can recombine with exogenous retroviruses to form recombinants with altered host range and pathogenic properties, thus posing the threat of species jumping, and disease ERVs also represent a potential threat as insertion mutagens or activators of oncogenes in the host species because of their ability to function as mobile transposable genetic elements capable of causing dysregulation of gene function, resulting in germ line mutagenesis and tumorigenesis.

Among endogenous retroelements that retain some degree of function, many have adapted and have become symbionts in their host species. Envelope genes derived from ERVs have been employed by their human [8, 9], sheep [10] and mouse [11] hosts to facilitate placental morphogenesis. Another example of ERVs co-evolving with their hosts include the contribution of an ERV enhancer in altering the tissue specificity of a human amylase gene from pancreatic to parotid-specific expression, promoting salivary gland-specific regulation of this gene [12]. ERV promoters have been employed by their hosts as promoters to express host genes [13], or to facilitate specific splicing events [14]. Endogenous retroviral components can also contribute to host defenses against future retroviral invasions, as is the case for Fv1 in mice, and endogenous Jaagsiekte sheep retroviruses (enJSRV). The latter have been shown to block exogenous JSRV infection by receptor blockade or via association of enJSRV proteins with exogenous JSRV, forming viral complexes that are blocked from exiting the cell [15].

Since the first step in retroviral endogenization requires germ cell infection, the appropriate viral receptor must be expressed on the germ cell. The receptors that lentiviruses, such as HIV, utilize are not present on germ cells. It seemed initially that this genus of retrovirus is prevented from becoming ERVs. However, this has been demonstrated not to be the case as an ancient retrovirus was recently discovered in the genome of a European species of rabbit [16], potentially providing a means of studying the process of lentivirus evolution.

The recent discoveries of novel ERVs and ERV functions, as well as new insights into the biological processes involved in virus-host co-evolution, make this an exciting time for ERV research. The reviews that make up this issue of *Cellular and Molecular Life Sciences* emphasize the significance of the recent achievements in the field. We would like to thank all the contributors for sharing their expertise in their individualized areas of endogenous retrovirus research.

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