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Guest Editorial

THE STORY OF A POACHER-TURNED-GAMEKEEPER : A TWIST IN ANIMAL EVOLUTION

A retrovirus is an RNA virus. In a host cell, it typically replicates with the help of an enzyme - reverse transcriptase - to produce DNA from its RNA genome. The resulting DNA is incorporated into the genome of the host by an integrase enzyme. The virus thereafter replicates as part of the host DNA. Retroviruses are generally enveloped viruses and their genomes commonly contain three open reading frames (ORFs) that encode for proteins found in the mature virus. The proteins are: group-specific antigen (*gag*) that codes for core and structural proteins of the virus, polymerase (*pol*) that codes for reverse transcriptase, protease and integrase, and envelope (*env*) that codes for the retroviral coat proteins.

Most retroviruses infect somatic cells, but in very rare cases, exogenous retroviruses have infected germ cells of their hosts, resulting in stably integrated 'endogenous' retroviruses (ERVs). Some ERVs have passed to subsequent generations like any other host genes. There are ERVs that persisted in the genome of their hosts for millions of years. The continuous accumulation of new and newer ERV integrations over millions of years, that occurred by both reinfection and retrotransposition, resulted in the genomes of all vertebrates being markedly colonized by ERVs.

ERVs are generally infectious for a short time after their integration as they acquire many inactivating mutations during host DNA replication. They can also be partially excised from the genome by a process known as recombinational deletion. However, some ERVs are transcriptionally active and have maintained intact ORFs for some of the genes.

ERVs with transcriptional ability have raised the hope of a possibility that some of these elements are beneficial to their hosts and thus, they were selected. There lies the story of 'endogenization' of retroviruses with a twist: a poacher turned into a gamekeeper resulting in a win-win situation. Some ERVs in vertebrates were possibly selected for their ability to provide protection against infection of related exogenous pathogenic retrovirues through various mechanisms. In a number of mammalian species, ERVs have been shown to block viral entry of exogenous retroviruses by receptor competition.

The possible contribution of ERVs in mammalian reproduction is even more intriguing. During pregnancy in viviparous mammals, ERVs are activated and produced in high quantities during the implantation of the embryo. It

has been hypothesized that they possess immunosuppressive properties, suggesting a role in gestational immune tolerance, protecting the embryo from its mother's immune assault. Also viral fusion proteins apparently support the formation of the placental syncytium in order to limit the exchange of migratory cells between the developing embryo and the body of the mother. During evolution, it is possible that ERVs had a primary role in viral defence, but they were later co-opted to support placental development. It is likely that the ancestors of modern eutherian mammals evolved after an infection by this virus, enabling the fetus to better resist the immune system of the mother.

Human ERVs (HERVs) contribute nearly 8% to the human genome and composed with about 98,000 elements and fragments. In the human genome project, HERVs have been classified into 24 families. All appear to contain nonsense mutations or major deletions, thus they cannot produce infectious virus particles, and most of them had first integrated into genomic structure many millions of years ago, even before human beings evolved. However, there is one family of viruses that have been active since the divergence of humans and chimpanzees about 2-3 million years ago. This family is termed HERV-K and it makes up to 1% of HERV elements. There are indications that it has even been active in the past a few hundred thousand years only, as some human individuals carry more copies of the virus family than others. But the absence of known infectious members of the HERV-K family, and the lack of elements with a full coding potential within the published human genome sequence, suggests that the family is less likely to be active at present. However, some HERVs are suspected to be involved in some autoimmune disease conditions like involvement of multiple sclerosis-associated retrovirus (MSRV) in multiple sclerosis.

Studies performed by Doug Nixon and Keith Garrison at the University of California San Francisco, and by Mario Ostrowski and Brad Jones at the University of Toronto, documented evidence for T cell immune responses against HERVs in human immunodeficiency virus (HIV) infected individuals. They hypothesized that HIV may induce HERV expression in HIV infected cells, and that a vaccine targeting HERV antigens may specifically eliminate HIV infected cells. The potential advantage of this approach is that, by using HERV antigens as surrogate markers of HIV infected cells, it could circumvent the difficulty inherent in directly targeting notoriously diverse and rapidly mutating HIV antigens. If it works, ERVs shall be useful for human application.

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