

How many of our genes are actually human in origin? **David Griffiths** and **Cécile Voisset** explore the fascinating impact of endogenous retroviruses in and on our bodies.

Retrovirus infection represents perhaps the most intimate of all host–pathogen relationships. The replication of these viruses requires the insertion of a DNA copy of their genome into the chromosomal DNA of the infected cell. This process, known as integration, is essentially irreversible and provides a means for stable, usually lifelong, infection of the host. Moreover, if a retrovirus infects a sperm or egg cell, or their germ cell precursors, its genetic material can become permanently fixed in the germ-line DNA of any resulting offspring. In this way, the retrovirus can persist in the host and its descendants for millions of years. Such inserted sequences are known as endogenous retroviruses

(ERV) and they are replicated and inherited in a Mendelian fashion along with all other nuclear DNA.

Over the course of evolution, retroviruses have invaded the germ-line of our ancestors on numerous occasions such that human ERVs (HERVs) now comprise ~8 % of our genome. These can be divided into around 30 different families, each representing a different ancestral infection event. The timing of their introduction into the genome ranges from over 30 million years ago up to less than 1 million years ago, depending on the family. Since HERVs represent ancient infections, they are not closely related to retroviruses currently circulating in humans, such as HIV. Instead, they have greater sequence similarity with ERVs of animals.

◀ Common Gibbon (*Hylobates lar*). Many HERV integrations are also present in the same genomic locus in other primates, a feature which has been used to date the time of germ-line infection. HERV-W is common to Old World primates (e.g. chimpanzees, gibbons and African green monkeys) but is absent from New World primates (e.g. squirrel monkey) and is therefore thought to have entered the germ-line around 25–40 million years ago, the divergence time estimated from fossil records. Art Wolfe / Science Photo Library

▼ False-coloured TEM of an ultrathin section showing a group of HERV-K particles budding from a cultured human teratocarcinoma cell. HERV-K is the only HERV family known to encode assembled virions. These non-infectious particles are well characterized in cell lines derived from testicular tumours. Some recent studies have suggested that HERV-K has been capable of re-infecting the human germ-line relatively recently (<100,000 years), raising the question of whether a relative of this virus still circulates as an infectious virus today. Klaus Boller, Paul-Ehrlich-Institut, Langen, Germany

Human endogenous retroviruses: from ancestral pathogens to bona fide genes

Consequences of endogenization for the virus

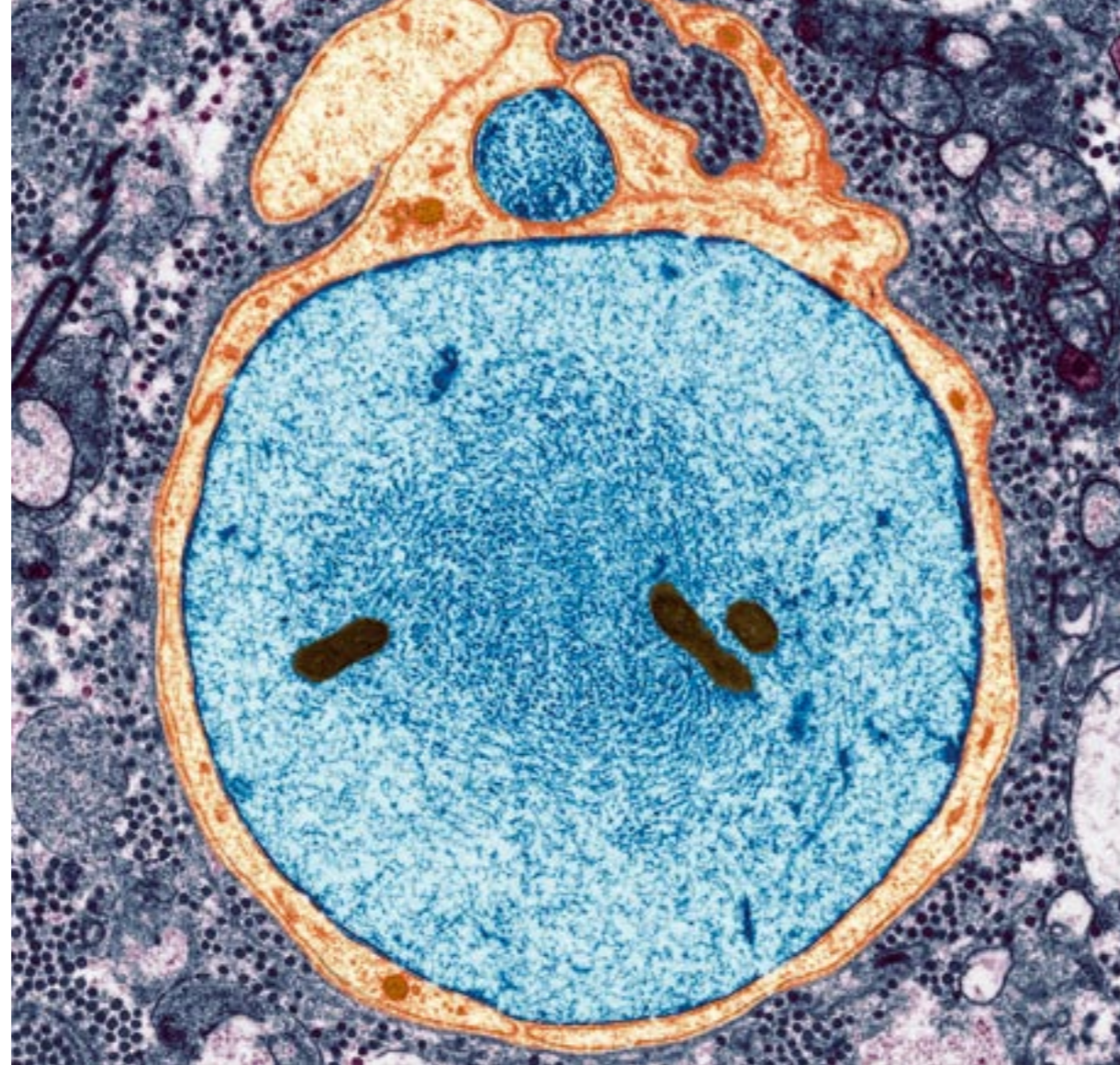
Because retrovirus infection is frequently pathogenic, any new introduction of ERVs is likely to be highly detrimental for the host. Therefore, to become fixed in a genome, a newly endogenized retrovirus would probably be inactivated to prevent its expression, for example through mutation or truncation of genes encoding viral proteins or by cellular mechanisms such as the silencing of ERV gene expression by DNA methylation. In this way, endogenization of retroviruses leads ultimately to their inactivation and a reduction in pathogenicity. Contemporary HERV families therefore consist of numerous heterogeneous elements, ranging from full-length defective proviruses to isolated long terminal repeats (LTRs) derived from recombination events. (LTRs are regions of the retroviral genome containing gene promoter and enhancer elements.) However, inactivation of ERVs may take many generations and the immediate effect of germ-line integration can therefore be increased pathogenesis, which could potentially lead to the extinction of the host. In humans, the effects of HERV acquisition on our ancestors millions of years ago can only be a matter of speculation. However, an epidemic of neoplastic disease currently afflicting koalas in Australia represents a modern example of retrovirus endogenization in action and provides a rare opportunity to study this process and its effect on the host.

While the vast majority of HERVs are defective, many are nevertheless transcribed as RNA in various tissues and in a few instances HERV proteins or particles may be produced. The abundance of HERVs raises the question of what effect their presence has had on the evolution of our genome and whether they have any function today. These topics have proved to be rather controversial, but recent work has provided some tantalizing evidence supporting roles in normal human physiology and also in disease.

HERVs as bona fide human genes

Among the rare HERV-encoded proteins, syncytin-1 and syncytin-2 are particularly interesting examples of how new functional genes may be acquired from HERVs in the human genome. Syncytin-1 and syncytin-2 are glycoproteins encoded by the envelope genes of specific proviruses of the HERV-W and HERV-FRD families, respectively. Of note, the other viral genes in these proviruses are highly mutated, suggesting that the genes encoding these envelope proteins may have been positively selected by providing some benefit to humans. The key biological function of these two proteins is their ability to mediate the fusion of cellular membranes to produce multinucleate cells or syncytia. Importantly, it appears that this function has been co-opted by the host to serve an important physiological function.

Syncytin-1 is expressed predominantly in placental cytotrophoblast cells where it participates in their fusion to form the syncytiotrophoblast. This is a fused cell layer that forms the



◀ Coloured TEM of a section through a demyelinated nerve in multiple sclerosis. The axon (blue) has only its Schwann cell (brown) surrounding it. The Schwann cell would normally produce the myelin sheath. A nerve's myelin sheath helps it conduct electrical impulses and when the myelin sheath is lost, nerve function is impaired. Steve Gschmeissner / Science Photo Library

direct border between maternal blood and foetal tissues, and its formation and maintenance is crucial for a healthy pregnancy. Dysregulation of syncytin-1 expression could impair placental morphogenesis and has also been linked with pre-eclampsia. Syncytin-1 induces the formation of cell-to-cell fusion by interacting with its specific receptors, the amino acid transporters ASCT1 and ASCT2. In non-placental tissues, syncytin-1 expression is usually kept silent through promoter methylation because inadvertent cell fusion could be deleterious for tissue organization and integrity. Syncytin-2, which has been characterized only recently, is also expressed in cytotrophoblastic villous cells and may serve a similar function in placental development. The HERVs encoding the syncytin proteins are only present in primates; however, unrelated ERV envelope proteins in mice and sheep have also been implicated in facilitating placental cell fusion. Given the divergent placental structures between these species and humans, this is a startling example of parallel evolution where unrelated retroviruses have been co-opted to serve a conserved host function.

Are HERVs still pathogenic?

Although individual HERV proteins, such as syncytin-1 and 2, may serve a physiological role for the host, expression of HERVs has also frequently been linked with diseases, notably autoimmune diseases and cancer. However, due to the ubiquity and abundance of HERVs, it has proved difficult to confirm or refute a role for them in pathogenesis. Nevertheless, recent evidence has implicated syncytin-1

in the aetiology of multiple sclerosis (MS). MS is a chronic inflammatory disease of the central nervous system, characterized by the loss of the myelin sheath that surrounds and protects neurons. The pathogenic mechanisms involved in MS are still unclear, but inappropriate expression of syncytin-1 in astrocytes has been proposed to exacerbate the inflammatory events within the brain and spinal cord by inducing inflammatory mediators such as interleukin-1 β (IL-1 β) and reactive oxygen species. These factors are cytotoxic for oligodendrocytes, the cells involved in myelin formation. What triggers the expression of syncytin-1 in the astrocytes is unknown but it has been shown that cytokines detrimental to MS, such as tumour necrosis factor, interferon- γ , IL-6, and IL-1 can activate the syncytin-1 promoter, while the MS-protective cytokine interferon- β inhibits syncytin-1 expression. Why this should occur in some individuals and not others is also unclear but common herpes virus infections of the central nervous system have been proposed as a potential initiating factor.

Research on other HERV proteins has focussed on their potential role in cancer because a number of malignancies are accompanied by increased production of HERV RNA and proteins. Some members of the HERV-K family, which integrated into our genome relatively recently (~1–5 million years ago), can express non-infectious particles. These defective viruses are expressed in melanoma, testicular tumours and myeloproliferative diseases, but whether they are actively involved in triggering or promoting tumour development appears doubtful. It is perhaps more likely that they are up-regulated as a result of other genetic lesions in the tumour cell. An exception may be teratocarcinoma where a HERV-K protein called Rec has been directly implicated in activating transcription factors involved in cellular proliferation. As with syncytin-1 and MS, additional research is necessary to determine its importance in tumour development.

An infectious HERV?

In some species, such as pigs and chickens, a few ERVs have escaped deleterious mutation and remain capable of infectious transfer. In humans no such virus has yet been described. However, recent work by laboratories in France and the USA has reconstructed infectious forms of HERV-K that represent the consensus sequence of the most recently acquired HERV-K viruses. The original HERVs are defective for replication but the consensus sequences, in which the effects of individual mutations have been 'averaged out', are infectious. These viruses therefore provide important tools for further analysis of the function of this ancient virus and its potential role in disease.

The future for HERVs

HERVs have been with us and our ancestors for millions of years and it is only recently that their abundance has been recognized and their functional significance begun to be elucidated. Whatever their function today, at the

time that they entered our germ line, their infectious counterparts may have been pathogenic viruses. As noted above, there are no HERVs closely related to the infectious retroviruses currently infecting humans, although ERVs related to lentiviruses have recently been described in rabbits. Could it be possible in the future that HIV will be tamed by endogenization?

David J. Griffiths

Principal Research Virologist,
Moredun Research Institute,
Pentland Science Park, Bush
Loan, Penicuik, Midlothian
EH26 0PZ, UK (t 0131 445 5111;
e david.griffiths@moredun.ac.uk)

Cécile Voisset

Postdoctoral Fellow, Inserm
U613, Faculté de Médecine et des
Sciences de la Santé, 29200 Brest,
France (t +33 2 98 01 83 71;
e cecile.voisset@univ-brest.fr)

Further reading

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