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Current topic

From ancestral infectious retroviruses to bona fide cellular genes: Role of the captured *syncytins* in placentation

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ABSTRACT

During their replication, infectious retroviruses insert a reverse-transcribed cDNA copy of their genome, a "provirus", into the genome of their host. If the infected cell belongs to the germline, the integrated provirus can become "fixed" within the host genome as an endogenous retrovirus and be transmitted vertically to the progeny in a Mendelian fashion. Based on the numerous proviral sequences that are recovered within the genomic DNA of vertebrates – up to ten percent in the case of mammals – such events must have occurred repeatedly during the course of millions of years of evolution. Although most of the ancient proviral sequences have been disrupted, a few "endogenized" retroviral genes are conserved and still encode functional proteins. In this review, we focus on the recent discovery of genes derived from the envelope glycoprotein-encoding (*env*) genes of endogenous retroviruses that have been domesticated by mammals to carry out an essential function in placental development. They were called *syncytins* based on the membrane fusogenic capacity that they have kept from their parental *env* gene and which contributes to the formation of the placental fused cell layer called the syncytiotrophoblast, at the materno–fetal interface. Remarkably, the capture of *syncytin* or *syncytin*-like genes, sometimes as pairs, was found to have occurred independently from different endogenous retroviruses in diverse mammalian lineages such as primates – including humans –, muroids, leporids, carnivores, caviids, and ovis, between around 10 and 85 million years ago. Knocking out one or both mouse *syncytin-A* and *-B* genes provided evidence that they indeed play a critical role in placentation. We discuss the possibility that the immunosuppressive domain embedded within retroviral envelope glycoproteins and conserved in syncytin proteins, may be involved in the tolerance of the fetus by the maternal immune system. Finally, we speculate that the capture of a founding *syncytin*-like gene could have been instrumental in the dramatic transition from egg-laying to placental mammals.

1. Introduction

During the course of evolution, vertebrates have been exposed to multiple waves of infection by retroviruses. Taking advantage of their remarkable capacity to insert their DNA into the genome of target cells, some retroviruses have integrated into the germline of their host. They were then inherited vertically from one generation to the next in a Mendelian fashion (Fig. 1). As a consequence of numerous amplification events, endogenous retroviruses (ERVs) now compose multigene families and occupy a substantial fraction of the genome of vertebrates (8–10% in humans and mice) [1,2]. In their overwhelming majority, these so-called "proviruses", not being subject to any selective pressure, have progressively become disabled by simple accumulation of mutations or deletions. As a result, among all the copies of a given ERV family, only a few elements may still be infectious in some host species, namely those that have been recently "endogenized" into the genome of their host and that are still able to replicate and integrate new proviral copies within the germline; this is for instance the case for the koala retrovirus (KoRV) [3], the mouse leukemia viruses (MLVs) and the mouse mammary tumor virus (MMTV) [4], or the endogenous jaagsiekte sheep retrovirus (enJSRV) [5]. In other rare cases, only some of the retroviral genes were preserved and have remained functional over several millions of years following ERV integration, whereas all other retroviral genes of the same age had degenerated

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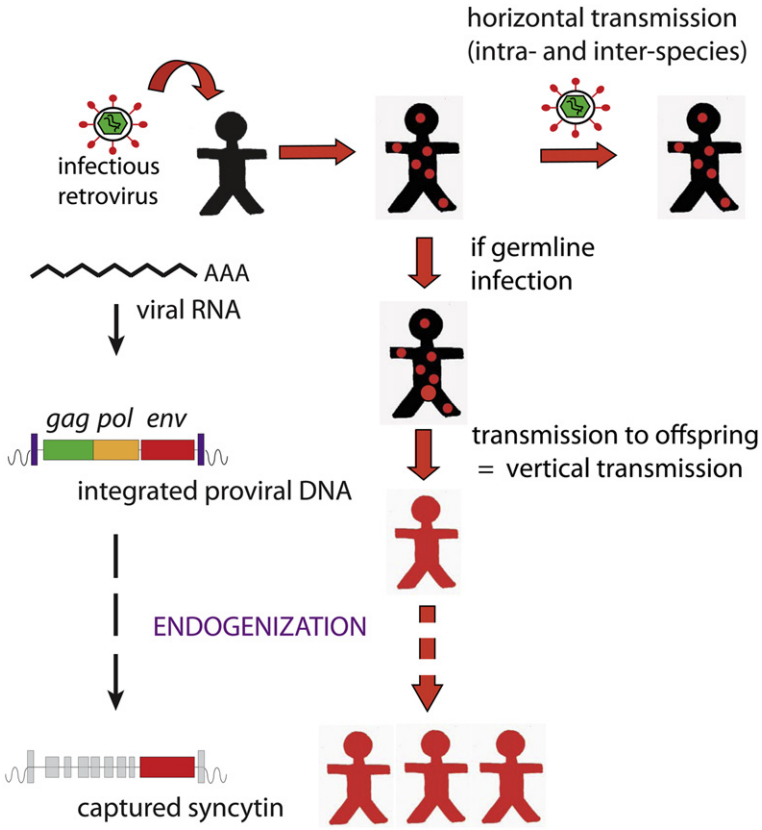

Fig. 1. Mechanism of retroviral endogenization. Retroviruses have the capacity to reverse transcribe their genomic RNA into a DNA copy which is then inserted into the genome of infected cells in the form of a provirus harboring the 3 viral genes *gag*, *pol*, and *env* (*left*). Retroviral infection of individuals leads to integration of the viral genome into a limited number of cells of the organism. Production of new infectious virions allows the horizontal transmission of infection, from one individual to the next (*top right*). In the rare cases where a retrovirus infects cells from the germline of its host, the integrated viral genome is transmitted to the progeny (*center*). The retrovirus has become endogenous and is present in all cells of the individual. During the course of evolution, most proviral genes are disrupted by multiple mutagenic events but occasionally one of them, such as the *env* gene exemplified here (*bottom left*), may be preserved and remains functional over several million years, contributing to the physiology of its host.

or had been lost. Conservation of ERV genes through evolution is highly suggestive of a selection pressure exerted by the host due to beneficial effects provided by such genes. A striking example of such a positive selection process is provided by the functional "capture" of viral *env* genes. Indeed, these genes, which encode the envelope glycoprotein of retroviruses, were found to have been selected in eutherian mammals for a key physiological role in placenta formation (Fig. 1).

2. Pleiotropic role of the retroviral envelope protein: from the virus replication cycle to a cellular biological function

The envelope protein of retroviruses plays a critical role for entry of the viral particles into target cells during the infectious cycle [6]. This protein is composed of two subunits assembled at the surface of infected cells and transferred to the virion during its budding at the plasma membrane (Fig. 2A). In the course of infection, the surface subunit (SU) positioned on the outside of the virion binds to a specific cellular receptor on the surface of the target cell. The virion-anchored transmembrane subunit (TM) triggers the fusion of the viral membrane with the plasma membrane of the target cells thanks to a fusion peptide (Fig. 2A, B) and the viral nucleocapsid is then released into the cytoplasm [6]. A few "endogenized" ERV *env* genes encode envelope glycoproteins that have kept some of the properties of the cognate proteins initially encoded by their ancestral infectious viruses, such as binding to a cell receptor, with decisive physiological consequences for the cells and the organisms where they are expressed. For instance, the retroviral *env*-derived murine genes, *Fv4* (*Friend virus susceptibility 4*) and *Rmcf* (*resistance to MCF virus*), and the ovine endogenous *enJSRV* ERV *env* genes confer resistance to infection by exogenous retroviruses by interfering with their receptors and limiting the availability of the latter at the surface of the cell membrane [5,7]. Moreover, in the same way as infection by some viruses – such as Human Immunodeficiency Virus (HIV) or measles virus – can drive the fusion of infected cell membranes [8], envelope proteins from ERVs expressed at the cell surface can induce fusion with a neighboring cell provided that the latter displays the appropriate receptor on its own surface. Such fusion can involve several adjoining cells leading to the formation of a multinucleated giant cell, designated a syncytium (Fig. 2B). Genes encoding fusogenic envelope proteins were identified for the first time within the human genome among members of the human endogenous retrovirus (HERV) families [9–11].

3. Occurrence of envelope protein-coding genes within the human genome

Exhaustive search within the human genome for *env* genes with long open reading frames (ORFs) disclosed only 18 genes encoding a putative envelope protein [12,13]. Among those potentially endowed with a function, the first to be described was the ERV3 protein, which is specifically expressed in the placenta and is encoded by a proviral gene conserved in the Hominid and Old