Genomic vagabonds: Endogenous retroviruses and placental evolution

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Endogenous retroviruses (ERVs) appear to have a particular predilection for placentas: retroviral genes have repeatedly been coopted for placental functions. In this issue, Chuong draws attention to the important contribution of retroviral promoters in rewiring placental development [1]. He proposes that trophoblast cells provide a permissive epigenetic environment for ERV activity because placental development has become "addicted" to transcription from ERV-derived promoters. In this view, adaptations to shut down ERVs in trophoblast cells are unable to evolve because they would also inactivate key developmental pathways that use retroviral-LTRs as promoters. In a process of positive feedback, past cooption of LTRs favors continued ERV activity that predisposes to new cooption of LTRs and reinforcement of the addiction. This recursive process could help to explain the extraordinary diversity of placental structures among eutherian mammals.

By definition, ERVs are inserted into germline DNA and inherited by every cell of the body. They can be transmitted vertically by replication with host DNA at existing loci or horizontally by insertion at new loci in the soma or germline of the same or other organisms. At each locus where it is inserted, an ERV is subject to the same selective forces as surrounding DNA, including selection to suppress horizontal transmission. Thus, vertical transmission selects for defective retroviruses but horizontal transmission selects for transposition-competent retroviruses. Because the horizontal and vertical "fitnesses" of ERVs are negatively correlated, mutations that reduce transposition will accumulate at existing loci at the same time as mutations that enhance transposition and infection relocate to new loci.

ERV sequences that exist at high frequency at a particular locus have proliferated by vertical transmission. Such sequences must provide a host advantage or be the lucky beneficiaries of drift (random sampling in small populations) or draft (hitchhiking with a nearby positively selected site). High-frequency ERVs are unlikely to have strong negative effects on host fitness and are unlikely to encode infectious retroviruses. For an ERV to have maintained adaptations for vertical transmission, its ancestors must have constantly changed location to keep one step ahead of inactivating mutations. At each particular locus, disease-causing ERVs will be rare and rapidly eliminated by natural selection.

Placental expression would be adaptive for ERVs if it enhanced their horizontal transmission. One intriguing possibility is that ERVs inherited via sperm and released from placentas could infect mothers or siblings [2]. Such a route of contagion could be mediated by classical retroviral particles or by exosomes released into the maternal circulation to fuse with maternal cells. Two recent papers report that syncytin 1, encoded by a domesticated retroviral *envelope* gene, is present on the surface of human placental exosomes [3, 4] and may facilitate fusion with maternal cells. In additional to a possible cargo of ERVs, placental exosomes have been shown to carry imprinted (paternally expressed) microRNAs [5] that may modify maternal physiology for fetal benefit.

The "parasitic" lineage that is an infectious ERV leaves new host DNA behind at each step as it rambles through the genome. Much of this incremental DNA will be deleterious and rapidly eliminated by natural selection. However, the occasional insertions that provide new host functions will be retained. Such rare events may be an evolutionarily important consequence of retroviral activity, but they are not the *raison d'etre* of that activity.

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