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Author
Villarreal, Luis P

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REVIEW ARTICLE

Viruses and the placenta: the essential virus first view

LUIS P. VILLARREAL

Center for Virus Research, Department of Molecular Biology and Biochemistry, University of California Irvine, Irvine, CA, USA

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A virus first perspective is presented as an alternative hypothesis to explain the role of various endogenized retroviruses in the origin of the mammalian placenta. It is argued that virus–host persistence is a key determinant of host survival and the various ERVs involved have directly affected virus–host persistence.

Key words: Virus evolution; host evolution; placenta; endogenous retroviruses.

Luis P. Villarreal Center for Virus Research, Department of Molecular Biology and Biochemistry, University of California Irvine, Irvine, CA 92617 USA. e-mail: lpvillar@uci.edu

THE PROBLEM – WHY SHOULD ERVS CONTRIBUTE TO THE COMPLEX PLACENTAL NETWORK? CONFRONTING THE ACCEPTED VIEWS

The emergence of mammalian vivipary and the placenta presents many biological and behavioral issues that challenge theories of evolution, see (1). These biological and immunological dilemmas are associated with the emergence of the 'foreign' mammalian placenta (expressing paternal genes). In addition, the very first cell type to differentiate in mammalian embryo is the trophectoderm which will generate the placenta, thus major alterations to programs of early developmental are also needed. The placenta will mediate the blood (and immune) exchange between mother and her non-self embryo and contribute to very complex biological and behavioral changes needed for live birth. All these changes require complex and network based regulatory changes to the genetic programs that had mostly been present in ancestral egg laying mammals. This represents a major transition in the evolution of complexity that has been difficult to explain by traditional concepts. Over the years, it has become increasingly evident that endogenized retroviruses (ERVs) have been intimately and deeply involved in the placenta of all mammalian lineages (2). These historic retrovirus observations include the presence of intercisternal A-type particles (IAPs) (3), presence in human oocytes (4), presence in early preimplanted embryo (5), antivial activity of human sera (6), the presence of reverse transcriptase (RT) inhibitors (7, 8), and the presence of ERV3 mRNA (9, 10). For a summary of these early observations see (11). In 1997, I proposed some general reasons why virus should be involved in the origin of vivipary (12). ERVs associated with mammalian reproductive biology are lineage specific and their acquisition is associated with the origin of each lineage (13, 14). But it was the discovery of the involvement of ERV envelope proteins (such as syncytins) in reproductive biology that has really engaged the interest of many evolutionary biologist in this virus–host relationship. Overall, they have adopted a now well accepted perspective that retroviruses have repeatedly provided *env* genes which have proved useful (were exapated/domesticated) for the various functional and structural requirements of a placenta (15–18). And once the early *env*-mediated placenta emerged, fitter (better) versions of placentas via newer ERVs followed. This is the currently accepted perspective on ERV involvement in the origin of the placenta and it presents a 'host come first' perspective. Here, the fortuitous virus is simply providing a convenient and diverse source of useful *env* genes. But, egg-laying animals (especially avians) are highly successful and diverse, so why viruses might mediate such a drastic change in reproductive host

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biology remains an open question. In this essay, I present a virus first perspective that offers an alternative hypothesis for virus involvement in the origin of the placenta.

A VIRUS FIRST PERSPECTIVE JUSTIFIED: VIRUS PERSISTENCE AND DISTINCT SOCIAL (NETWORK) FEATURES

It has been 10 years since I published my book which was first to present the evolution of life from a virus first perspective (19). If the main thesis of that book can be stated in simple terms it is that we must first consider the virus–host relationship with better understand evolution of the host. From this perspective, we can then see that viruses were involved in most all major transitions of host biology in evolution. This will likely seem an overstated or even preposterous position to most readers. How could genetic parasites (viruses) be providing such fundamental capacity for host evolution? And why would they do so? But we have come to recently realize that viruses are omnipresent so all life must survive in its virosphere habitat. And such survival often involves virus themselves since virus, their defective and various other genetic parasites (mostly called transposons) can and often do provide virus resistance systems. These viral colonizers then can also be used to provide new sources of host complexity (such as the placenta). Thus, to understand the deep role virus plays, we must always consider a virus first perspective for the evolution of complexity in the host. Essentially, the concept is that viruses are fully competent agents and editors of all host systems of instruction (DNA, RNA, epigenetic, translational etc.) (20). Thus, they provide the host with new sources of instruction systems (not errors). In addition, they promote network formation by providing coherent societies (quasispecies populations) of agents able to edit host code content (and add new identity) in a diffuse, distributed manner, which promotes the creation of and editing of host regulatory networks. Thus, a viral role in the origin of the placental regulatory network can be expected (21). Viruses possess all the advantages of evolution relative to host: extreme genetic adaptability, extreme diversity, extreme numbers, extreme rates of genetic exchange, tolerance for 'unfit' variation, and the ability to reassemble from cryptic or 'dead' parts. They can transition between the chemical and living world. Thus, I am asserting that most initial genetic and selective events that transform host regulatory complexity are usually 'pushed' by virus action in a general direction of increasing complexity. In this way, viruses present an omnipresent and ancient issue. Hence, we must always consider how any virus action on host will affect virus–host survival in their respective virosphere or virus habitat (e.g., reproductive tissue). A most significant development would be the emergence of a stable persistent relationship between virus and host as this represents a virus–host symbiosis that now protects the host form the same and often other lytic (disease causing) viruses. Persistence is difficult to attain not the indirect result of survivor of runaway (selfish) replicons. Persistence inherently requires self-regulating and self-opposing functions. Thus, even 'defective' (and parasitic) components of viruses (and transposons) can express virus-specific regulatory (opposing) molecules (including ncRNA), clearly promote virus–host persistence, and respond to oppose lytic virus infection. Thus, the presence of incomplete viral elements in host genomes are not simply the remnants of past viral infection and disease (virus sweeps), but should be considered as the savior of the host lineage by providing the capacity for self regulation and persistence of viruses that can still threaten related species. Virus persistence provides a large selective advantage in the virosphere. It also presents a perspective that is essentially the converse of the current view in evolutionary biology: viral persistence is a big determinant of host survival with strong effects on host group survival as well (via virus communication) (22). It defines a relationship between virus and host and between host themselves that does not adhere to the predator–prey theory (23, 24). Nor does it adhere to the red-queen hypothesis. Persistent virus is usually highly prevalent, silent, often genetically stable, co-evolving with the host and usually transmitted from parent (old) to offspring (young) or in close coordination to host reproductive biology. Establishing persistence is difficult and can be thought of as resulting from a successful hacking of host identity networks to insert new code and promote survival of a new more complex virus–host identity. Since persistence is always regulated, it is a mostly silent state in which reactivation is tightly linked to host (reproductive) biology with big consequences to host and virus fitness. This makes it much more difficult to study. Asserting the core importance of persistent virus to host survival thus presents a big break from historic views in evolutionary biology and adds a process of selection that stems from the horizontal transmission of persistent virus. As the virosphere provides no 'virus-free' habitat for any life form, all living forms have adapted to their own viral habitat.

APPLYING THE VIRUS FIRST PERSPECTIVE TO PLACENTAL ORIGINS

Let us now conceptually reconsider the placenta from this virus perspective. Accordingly, 'exapted' viral *env* genes were not initially a convenient source of genetic errors for promoting a more efficient placenta, but instead they were successful colonizers that allowed the host lineage to control various persisting viruses prevalent in their reproductive systems. The absence of these ERVs (*envs*) would leave these host susceptible to these same and/or other viruses (25). In this light, the presence of an impervious eggshell would preclude the colonization of the shell membrane by active and self protective virus. But by creating a virus accessible and rich tissue (trophectoderm; exposed after zona pellucida loss) which is needed for host reproduction, it promotes virus-based network solutions (e.g., genetic reprogramming, immune suppression, transformation, membrane fusion) to biologically difficult problems needed for vivipary to emerge (12). In addition, the new virus–host symbiont has acquired a very significant advantage compared the uncolonized host that remain susceptible to the disease induced by related viruses. By modifying host identity (and immunity), these ERVs have thus set the stage needed to promote virus persistence as well as a new host reproductive strategy. This reproduction strategy must in turn promote the reproductive success of the new virus–host combination. However, the ERV-host relationship is often dynamic and can continue to be susceptible to subsequent (competing, displacing) ERV colonization as the persistent/acute virus habitat further evolves [as an exemplar, see JSRV (26)]. Wild mice show similar strain (mating) specific ERV-cancer biology (27, 28). This virus first scenario can thus provide an answer as to 'why' various distinct, but, host lineage-specific viruses have been involved in their placentas and promote more complex host reproductive biology. These viruses thus resemble a competent, but, diverse gang of highly effective network hackers that seek to add new (viral) instructions. Because viruses can also disperse and interact as populations [quasispecies: QS, see (29)], viruses can modify distributed regulatory networks, not simply a specific loci or individual host. Such network editing need not occur by a serial set of individual events involving master individual type virus selection (30). They can instead involve quasispecies-based and defective virus-based processes that occur via population based virus colonization (see the Koala-virus example below). Such diversity makes these agents prone to multifunctional-, conditional-, and context-dependent interactions. Indeed, the QS-based feature of RNA viruses in particular, allows us to think about the involvement of a virus 'consortia' as natural editors of host genetic content (31). Thus, the presence of such distributed virus-derived (often defective) information is not the residual product of errors, but the product of a QS-based colonization that directly affected virus persistence, virosphere survival, host competition, and has also modified host identity systems. Host evolution is then free to adapt these new viral network systems for host reproduction and survival. Successful virus colonization of host thus promotes new complex host group and individual identity that strongly affects competition with related, but, uncolonized host populations and leads to a modified virosphere.

AN EXAMPLE OF ONGOING POPULATION-BASED ENDOGINAZATION: KOALA RETROVIRUS

Let us now outline some evidence that is most relevant to this virus first scenario: that is, virosphere survival via persisting new virus information. The Koala's of Australia provide a particularly recent, relevant, and informative story, see (32). Koalas have recently undergone an epidemic of retrovirus (KoRV, a gamma retrovirus)-mediated leukemia. Survivors, however, are undergoing endogenization by an array of this same virus [which itself appears to originated from an virus of rodents or bats (33)]. Survivors do not die from leukemia, but they can generally still produce the virus, which is now held in check by the endogenized (proviral) versions. Thus, they have established persistent infections with low disease. This endogenization is occurring by a complex process involving geographically (and tissue specific) distinct populations of both exogeneous and endogenous viruses involving an increasingly large diversity of ERVs at low copy level (34). Clearly, the endogenized KoRV must modify the exogeneous KoRV-induced immune cell dis-regulation (leukemia) that would otherwise occur. Indeed, wild Koalas with endogenized KoRV no longer make antibodies to KoRV (33). Thus, virus information has become 'one' (symbiotic) with host and must be involved in virus control. But not all Koala populations have been equally affected by the epidemic. Populations isolated in some islands have much less disease and no endogenization. However, it would not be difficult to predict what might happen if the persistently infected mainland Koalas now come in close contact with these isolated populations: survival of the persistently infected. This new Koala KoRV virosphere requires that these

ERVs must remain in Koala genome along with their capacity to cause tumors in non-endogenized populations. Thus, inducing lethal tumors (viral harm) is not a breeding artifact but an important phenotype that can be transmitted to compel uninfected Koalas to either die or become one (persistent) with KoRV. This situation promotes reproductive isolation via the survival of KoRV endogenized Koalas.

GAMMA ERVS IN BATS, INTERACTION WITH OTHER VIRUSES, AND REPRODUCTIVE ISOLATION

Gamma retroviruses viruses (in contrast to lentiviruses) have been very successful in endogenizing vertebrate species (as sources of ERVs). Gamma retroviruses are mostly transmitted from old to young, often via reproductive tissue. Indeed, the reproductive tracts appear to generally provide a 'virus-rich' and also a 'virus-mixed' habitat. Thus, we might also anticipate that the placenta will need to provide general mixed virus resistance and that such resistance will often be mediated by resident or endogenized virus, as has been reported (35). Gamma-retro virus endogenization has also occurred in bats (36). Interestingly, ERVs seems to have also been involved in (helped) the endogenization of filoviruses (Ebola and Marburg) that has also occurred in bats (37). Given the capacity of bats to host many persisting RNA viruses that are highly pathogenic to other species, their significant genome colonization by the gamma retroviruses and rolling circular DNA virus defectives (expressing stem-loop miRNAs) is particularly interesting (38). Such persistence by potentially lethal virus is not simply due to the fortuitous containment of an infection, but must have resulted from the establishment of a virus 'addiction module' in that the same defective virus must resist similar virus. But if the host were to lose this (defective) virus information, it too would become susceptible to lethal infection. This, I suggest, defines a general issue that applies to all species and their viruses. It also can explain the emergence of sexually incompatible populations (due to incompatible persistent viruses). It is furthermore likely that this issue also relates to sexual incompatibilities seen via methylation (39). Virus persistence (addiction) is not specific to ERVs. In wild mouse colonies, for example, many viruses can establish prevalent and highly stable persistent infections, including MVM, MPV, Theilers virus, LCMV, MHV. Although some of these viruses are also capable of causing disease (even in wild colonies), they are often held in check by population-based 'virus persistence', for example via maternal antibodies transmitted through the placenta at birth (40). Generally, such persistently infected wild colonies are healthy. Yet the introduction of such wild mice into uncolonized 'virus-free' breeding colonies will usually result in reproductive collapse of the entire virus-free colony. Thus, the history of persisting virus in a specific population can have measurable and large survival consequences. Along these lines, we can consider the recent Ebola virus epidemic. Human male survivors appear to persistently produce viruses in reproductive tissue (41). Clearly, such persistently infected and sexually transmissible humans pose a major risk to all extant human populations. In contrast to rodents and bats, humans host a lot of persistent DNA virus infections (polyomavirus, papillomavirus, adenovirus, herpes virus). Many human-specific viruses can also be found in the reproductive organs. Herpes 6/7 and HSV-2 are especially present in such tissues (42) and able to cause fatal encephalitis in unprotected newborns (via non-immune mothers) (43). Interestingly, these HVs persist via microRNAs that modify host apoptosis (44) and can act cooperatively (45). HHV 6 can also integrate into chromosomal (centromere) DNA and allow genomic maternal to fetal transmission (46). And the presence of such prevalent viruses in human reproductive tissue can have major consequences to other viruses, such as HIV-1. Indeed, in the S. African epidemic, heterosexual transmission of HIV-1 depends heavily on co-infection with HSV-2 (47). A similar situation applies HIV-1 and papillomavirus-induced cancers (48). Some viruses can inhibit HIV (49). Interestingly, HERVK serum immunity can also affect HIV (50). Thus, the reproductive tract provides a virus-rich and mixed-virus habitat.

VIRAL IDENTITY AND IMMUNE NETWORKS VIA PARASITE DERIVED STEM-LOOP RNA

The importance of small non-coding RNAs for DNA virus persistence has recently become clear (51). But small non-coding RNA regions (with stem-loops) are also the main identifying and regulatory elements for most if not all RNA virus. Indeed, the definition of a gamma retrovirus depends on such a stem-loop element. Also, within retroviral LTRs and various other crucial control elements, stem-loop RNA are essential for identification and regulatory function. Thus, RNA–RNA interactions via stem-loop regions promote the establishment of RNA-based regulatory networks. Other parasitic retro-agents (LINEs/SINES, alu's)

can also be transcribed to produce non-coding stem-loop RNAs. This suggests the possibility for an extensive and mixed system of RNA-based regulation all deriving from parasitic agents (52). From the host perspective small non-coding RNAs are mostly thought to control host–virus (retroposon) interaction (53). Indeed, many human microRNA's target retroviruses and ERVs (54).

MULTIFUNCTIONAL NETWORK ISSUES FOR THE PLACENTA SOLVED BY ERVS

Let us now further consider a virus first (virus-origin) perspective for the origin of the placenta. Accordingly, virus should: (i) be involved the origin of the trophectoderm (first embryonic cell to differentiate), (ii) promote embryo implantation, (iii) promote complex placenta functions (including the cellular interface and invasion that feeds the embryo), (iv) regulate the mother's (host) immune response, (v) communicate to reprogram the mother's (host) physiology and behavior to support the embryo during pregnancy and after birth. These may seem like impossible and overly diverse tasks for viruses to help solve. This is on top of the fact that prior egg-based reproduction must have already been working well. But let us recall the general competence of virus to regulate all systems of host control, including all genetic, epigenetic, transforming systems via a process involving transmissible-, diffuse-, ERVs-, and ncRNA-based regulation. Such new regulations can be forcefully superimposed onto the host. Viruses are good for this. In the next section (on Motherhood behavior and virus), a related complex issue of virus–host reproduction reprogramming in the context of parasitoid wasps is also presented, but involving distinctly different DNA viruses. With respect to the placenta, there is indeed evidence of viral (and antiviral) involvement in all of the above issues. Retroviral and retroposon RNA is highly expressed and regulated in the early embryo. And although DNA methylation is thought to restrict retrovirus and retroposons, stem cells (and the placenta) are open to ERVs as their DNAs are hypomethylated (55). lncRNA, siRNA and RNAi are all involved in early embryo regulation but are also either derived from retroposons or thought to regulate ERVs and retroposons. The RNAi system in invertebrate animals and plants is a core innate immune regulator of virus infection. Yet, its antiviral function was mostly lost in jawed vertebrates along with the emergence of the interferon system and adaptive immunity. Interestingly, it retains activity in the early embryo and is needed for early development (56), but is not apparent in most somatic tissue. This strongly suggests a major alteration to antiviral systems occurred in early mammalian embryos. Also, lncRNA appears to be involved in early embryo programming, but such RNAs are mostly derived from retrotransposons (57). Other expressed functional repeat RNAs are also derived from retrotransposon (58). Indeed, ERVs themselves appear to be directly involved in fetal imprinting (59). Subsequently, embryo implantation involves reverse transcriptase activity that is derived from retroposons (60). In addition, the placenta clearly depends on the various ERV env (syncytin) genes for both structural and functional needs (61). And at least ten lineages of mammals have acquired their own version of *envs* for placental function. But the regulatory regions for these syncytins is complex and composed of mixtures of LTRs and other regulatory regions derived from other retroviruses (62). Indeed, the placenta does not seem to emerge from the acquisition of a lot of new genes, but instead appears to result from a more complex regulation of mostly previously existing genes via a the emergence of a regulatory network that was derived to a large degree from ERV-LTR elements (63). These LTRs may be providing enhancer-based gene regulation (64). In addition, LTR regulation of insulin (65), poly-A control (66), NOS3 expression (67) have all been reported in the placenta. The acquisition of such regulatory complexity in the placenta along with its coherence clearly present a big problem. How can we explain the origin and integration of this network? A selective process involving serial individual fittest type selection (exapted genes) does not account well for how network coherence (cooperation) is attained. Indeed, I think such step-wise selection is not possible given the successive and long durations needed for differential offspring survival and also the clear similarity of viral elements to be distributed in the network in order for the placental to be formed and function. However, if instead we invoke a process similar to what is occurring in Koala ERV endogenization, we see evidence for population (network)-based colonization *en mass*. For this to occur via the placenta, the placenta must have been initially involved in viral and antiviral control, as has been reported (35). Indeed, both network emergence and antiviral status should associate with ERV acquisition. And other human viruses, such as HIV, HSV, could also be affected (68).

PLACENTAL VARIATION AND CORRESPONDING ERVS

Biologically, the placenta varies greatly between species (69), especially its invasiveness (70). The

selective pressure and molecular basis for such variation has always been curious and difficult to explain. However, if we consider the involvement of distinct viral ecologies and colonization histories in placental origins, we might better explain such placental variability. Endogenous viruses (often defective but some expressing *env* or *gag*) can clearly provide restriction factors that limit exogenous virus susceptibility (71, 72), especially *env* (73). Such restrictions, however, are highly species, strain, and virus specific. The sheep retrovirus (JSRV) seems to provide the best model for how a virus is able to both infect as exogenous disease causing virus yet be essentially required for reproduction as an endogenized virus (74). Such a relationship can establish a dynamic, ongoing change to host ERV composition with degradation of older displaced copies similar to that as seen in primates (75). This JSRV model, I suggests, captures the essence of the virus–host dynamic in reproductive tissue. Reproductive transmission of virus becomes key. Indeed, various other animals show reproductive virus transmission and ERV changes, such as drosophila (76). However, it is clear that many species are unable to produce an exogenous virus from endogenous copies, such as primates. Clearly, there are distinct variability in species-specific virus–host composition and ecology. In many situations, I propose that it is likely that other viruses of the reproductive tissue are also involved in the placental-ERV relationship. Thus, the ERVs expressed in placental tissues may need to be evaluated in the context of additional virus mixtures and could have a more generalized antiviral affect.

ERV-DERIVED SYNCYTINS AND GENERALIZED ANTIVIRAL ACTIVITIES

Recently, the presence of syncytin-like ERV *env* in marsupial reproductive tissue has been reported (77). Marsupials have simple short-lived placentas in which embryos implant for periods of about 1 week, then the embryo is rejected from the interface and must feed off of the pouch secretions. This simple placenta is much less invasive and long-lasting then that of mammals and it also does not promote the exchange of blood (and antibodies) between mother and embryo. Yet even in this simplified placenta it seems an ERV *env* gene were needed to solve the interface problem posed by embryo implantation. Why might a virus also provide a good solution to this simplified biological situation? Many ERVs that produce *env* genes in reproductive tissue are dynamic and changing on an evolutionary time scale (75). If we adopt a virus first perspective to this situation, we could expect that an initial and new ERV colonization resulted in a more stable persistent relationship between virus and host reproductive tissue, but that such a state will often involve the emergence of a new antiviral state and will occur via diffuse (Koala-like) network-like mechanisms. The resulting virus–host combination can still be subjected to further successful ERV colonizations that similarly further alter antiviral states and regulatory networks. In this light, the recent report regarding the expression patterns of HERV-K in human reproductive tissue (early embryos and placental cytotrophoblasts) is especially interesting (78). This ERV (*env*) does not function as a syncytin, so *env* gene exaption is not a possible explanation for its presence. Also, these particular HERV Ks are relatively new and exogenous additions to the human (but not chimpanzee) genome, previously thought to provide no gene function to humans due to polymorphisms. But now it appears that this HERV K has provided virus restriction factors (*eng, gag*) that are also important for embryo function and it has also induced a more general antiviral state via the IFITM1-specific interferon response that more generally inhibits other virus replication. This general response is operating thorough the HERVK-encoded *rec* gene (a rev-like RNA transport protein) that interacts with stem-loop viral RNA regions. In these specific embryos, however, about 1/3 of cellular mRNAs have 3′ UTRs that can bind this *rec* and promote ribosome occupancy. Thus, HERVK has promoted the emergence of a new regulatory translational network in these human cells as well as a generalized antiviral response. Indeed, it has been previously observed that HERVK can also interact with other viruses. For example, HIV infection activates many human-specific HERV-Ks found at centromeres (79). In addition, HCMV has been reported induces HERVK (80), as has EBV (81). The relationship between ERV *envs* and host is thus complex (82). But their ability to induce general antiviral immunity as well as edit existing host regulatory networks seems established.

MOTHERHOOD, BEHAVIOR, AND VIRUS?

In an early paper I compared the role of ERVs in mammalian reproduction to that of polydnaviruses in the reproduction of parasitoid wasp (12). In both motherhood and wasp embryo parasitization of caterpillars, the host (caterpillar or mother) must be able to support an embryo that is foreign. Both these situations have some surprisingly similar sets of biological issues to overcome, including immune

suppression of host, altered genetic program to support (feed) the embryo and altered development and behavior of the host. And in both situations, endogenized viruses provide solutions to these complex problems. In the parasitoid wasp, the supercoiled closed circular DNA's that are packaged into VLPs are now accepted to have been clearly virus derived (83). This complex set of distributed viral genomes have become endogenized, are mostly defective and are expressed exclusively in female wasp reproductive tissue. Relatively few viral ORFs are expressed from these circular DNAs. Indeed, most DNA segments have repeated sequences within them. Interestingly, a differential microRNA response is seen in response to parasitization (84). What is particularly fascinating about the parasitoid wasp is that in some situations, the parasitized host caterpillar becomes immobile after the wasp parasites exit its body. The caterpillar, however, is induced to protect these wasp larvae by making a cocoon for them and guarding them against other parasitoid wasp species, before the caterpillar dies. The mechanism by which this dramatic behavior is induced is not understood. It seems likely, however, that the polydnavirus is involved. Given the paucity of polydnaviral ORFs, I would guess that regulatory RNAs are also likely to be involved. In mammals, mothers must also undergo major behavioral changes. Indeed, some increase in maternal brain size occurs during pregnancy. It has been proposed that a general link to brain size is due to mother–off spring bonding (85). It is also apparent that genomic imprinting essential for maternal brain development (86). Many of these changes are thought to be mediated by the placenta, thus trophectoderm and the placenta are likely sources of maternal behavioral control. Unlike the fertilized parasitoid wasp egg, which is surrounded by polydnaviral VLP layer, the surrounding placenta of mammalian embryo provides

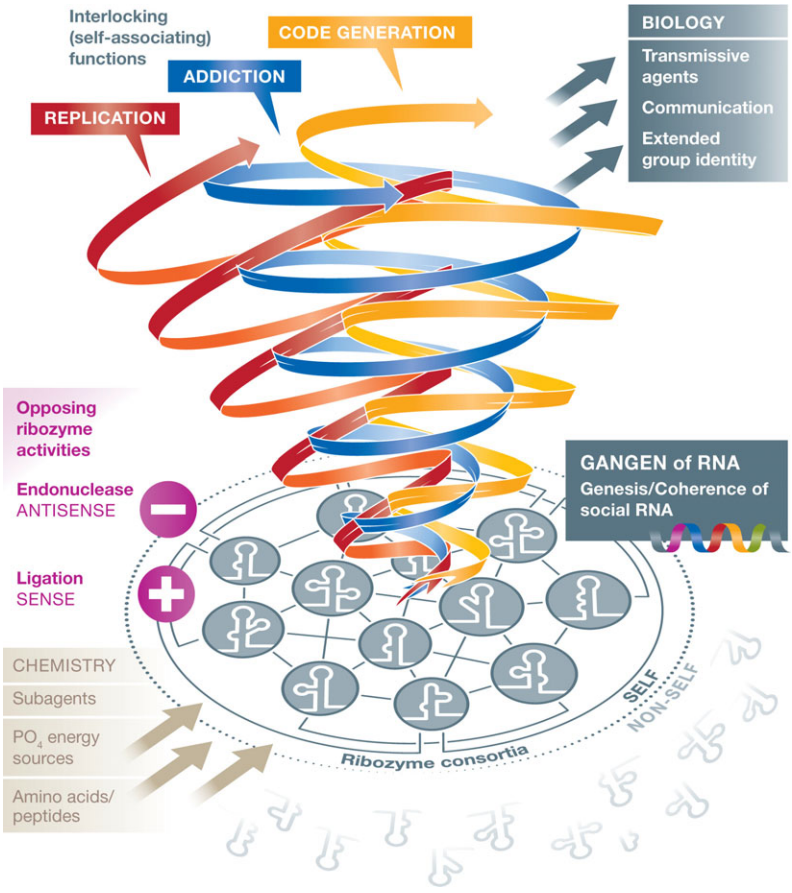

Fig. 1. The RNA gangen hypothesis: group identity and cooperativity of an RNA collective that requires opposite functions for the genesis of life (social behavior of agents). Reprinted with permission from Villarreal, Luis P. 2015. 'Force for Ancient and Recent Life: Viral and Stem-Loop RNA Consortia Promote Life'. *Annals of the New York Academy of Sciences* 1341 (1): 25–34.

much of the endogenous virus (ERVs) required for reproduction. A question that arises is if these human ERVs might also be involved in controlling the behavioral changes of motherhood. Is the placenta using ERVs in some way that alters the mother's physiology and behavior? As the mechanism by which maternal brains are modified by the placenta are not understood, we cannot answer this question. Yet it is clear that the placenta does use ERV products (*env* mediated budding) to communicate with other maternal tissues. The human cytotrophoblasts produce exosomes that have incorporated both syn-1 and syn2 (87). In addition, syn-1 containing blood borne exosomes can regulate the immune response (88). Also these placental exosomes incorporate miRNA (89).

TRANSMISSIBLE SMALL RNAS, ERV REGULATION AND MOTHERHOOD BEHAVIOR: EVERYTHING FROM VIRUS

Given that RNAi (dicer) is active in preimplantation embryos (56) and the ancestral role of miRNA in silencing retroposons in preimplantation embryos (90), ERV activity seems highly regulated by ncRNA and specific to the placenta. Indeed, maternal plasma has high levels miRNAs (91). And the placenta is a major site of secretion of exosome-containing micro RNAs (92, 93). Given the ability of miRNAs to control anxiety (94), a crucial maternal behavior, it thus seems plausible these *env* (syncytin) expressing exosomes are involved in regulating maternal behavior. Along these lines, the large human-specific C19MC miRNA cluster is one of the sets of miRNAs expressed in exosomes and this cluster is also imprinted in placenta (95). But this primate-specific C19MC cluster is also expressed in fetal brain and its induced overexpression strongly associated with pediatric brain tumors, see (96). Thus, there seems to exist a clear pathway for the ERV mediated placental control via ncRNA's of maternal brain growth and behavior. The relationship of a mother to her offspring is often considered in the context of mother–offspring conflict. Clearly, a parasitiod larvae is in a similar conflict with its caterpillar host. But as I have outlined above, in both situations endogenous viruses were involved in the origin (and resolution) of these embryo–host relationships. However, the survival advantage for the persisting virus involved, is seldom considered. Viruses have long been dismissed as simple selfish agents, not central to evolution. And their persistence has been treated as a trivial matter. Here, I argue that the virus perspective should instead be considered first. For the virus–host relationship (e.g., persistence) sets the stage for who will survive in the virosphere and what may follow regarding virus–host selection. In summary, viruses are competent in all biological codes and various forms of communication. And since viruses can often function as diffuse populations, they are capable 'hackers' of complex network systems not only able to reprogram a network but also to provide novel solutions, often via mixed and defective and counteracting viruses (via quasispecies). In their capacity to promote persistence, viruses also promote the infectious acquisition of systems of identity and immunity. Because viruses are transmissible, they affect the relationships (communication) not just within individuals but also to extended groups. This is the most powerful role. Indeed, I have recently proposed that a quasispecies consortia (*Gangen*) of transmissible stem-loop RNA's can better account for the origin of ribozymes and the identity and communication networks of RNA world organisms (97). See Fig. 1. From the origin of life to the evolution of humans, viruses seem to have been involved. Thus, the large scale expansion ERV LTRs and other stem-loop RNA elements (e.g., alu's) in the recent evolution of the human brain, might also indicate a viral role. So powerful and ancient are viruses, that I would summarize their role in life as '*Ex Virus Omnia'* (from virus everything).

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