Transposable element recruitments in the mammalian placenta: impacts and mechanisms

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Abstract

Transposable elements (TEs) are mobile DNA elements found at high frequency in mammalian genomes. Although these elements are generally perceived as genomic parasites, they have the potential to influence host genome function in many beneficial ways. This article discusses the role TEs have played in the evolution of the placenta and pregnancy in viviparous mammals. Using examples from our own research and the literature, we argue that frequent recruitment of TEs, in particular of retroelements, has facilitated the extreme diversification of tissues at the maternal–fetal interface. We also discuss the mechanisms by which TEs have been recruited for functions during pregnancy. We argue that retroelements are pre-adapted to becoming cis-regulatory elements for host genomes because they need to utilize host regulatory signals for their own life cycle. However, although TEs contain some of the signals necessary for host functions upon insertion, they often require modification before acquiring a biological role in a host tissue. We discuss the process by which one TE was transformed into a promoter for prolactin expression in the endometrium, describing a model for TE domestication called ‘epistatic capture’.

Keywords: transposable elements; placental evolution; regulatory evolution; prolactin; syncytin

INTRODUCTION

A strikingly high percentage of mammalian genome sequences are derived from transposable elements (TEs). Roughly half of the human genome, for example, is comprised of retroelements and DNA transposons, the two classes of TEs in eukaryotic genomes. Retroelements, which transpose to new genomic locations via an RNA intermediate, represent the vast majority of TEs in human and other mammalian genomes. TEs are often described as genomic parasites because of their ability to move, replicate and accumulate in genomes. Nevertheless, given their frequent occurrence, TEs (in particular retroelements) have the potential to impact host genome structure and function in a multitude of beneficial ways. These effects include altering gene regulation of host genes and donating new genes or exons to the host genome. The existence, location and frequency of different TEs can vary dramatically between species. Thus, TEs can influence the evolutionary trajectories of their host, with the potential to contribute to lineage-specific diversification and innovation [1].

When a TE is recruited for host function, the effect is often localized to a specific cell type or tissue. One organ that has been the site of frequent TE co-options is the placenta, making it a good system to study the mechanisms underlying and impacts of TE recruitments in the host. The placenta is a structure that enables the mother to directly provision developing offspring, via an apposition or fusion of fetal and maternal tissues. Here, we define the placenta as a composite of tissues at the maternal–fetal interface that includes both fetal (trophoblast) and maternal (endometrium) tissues. Marsupials and eutherian mammals use a placenta...
for fetal provisioning, but the organ was highly elaborated on in eutherian mammals. A striking feature of placental form and function in eutherian mammals is its high interspecific variation. The placenta is so diverse that Mossman [2] and others have described it as the most variable organ among mammals. The overall shape of the placenta, the type of interface between fetal and maternal tissues and the kind of interhemal barrier between fetal and maternal tissues (Figure 1) varies considerably between species, without a clear correlation between different aspects of placental morphology or between placental morphology and reproductive ecology (Figure 2). There is also considerable variation found at the molecular and cellular level, even among placentas with similar gross structure [3].

It has been suggested that co-option of TEs in both maternal and fetal tissues promoted the origination of placentation in mammals [4, 5]. Endogenous retroviruses (ERVs) have been implicated in the origin of invasive fetal tissues in early mammals [4]. Also, a DNA transposon, called MER20, is argued to have contributed to the origin of a novel gene regulatory network in endometrial cells of early placental mammals [5]. Lynch et al. [5] showed that many genes recruited into endometrial expression in placental mammals are located near a MER20 element. These MER20s have the epigenetic signatures of

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**Figure 1:** Characters and character states used to describe placental variation among mammals. (A) Placental shape, with states diffuse, cotyledonary, discoid and zonary (modified from Ref. [54]). (B) Interface/interdigitation between maternal and fetal tissues, with states folded, lamellar, trabecular, villous and labyrinthine (modified from Ref. [55]; This figure was published in Placenta, 1, Kaufmann, P., Functional anatomy of the non-primate placenta, pp. 13–28, Copyright Elsevier 1981). (C) Degree of fetal invasiveness, with states epitheliochorial (no invasion), endotheliochorial (moderate invasion) and hemochorial (high degree of invasion) (Reprinted by permission from Macmillan publishers Ltd: Nature Reviews Immunology 6: 584–84; Copyright 2006; see Ref. [56]).
Enhancers, insulators, and repressors and the genes associated with them are overrepresented for functions in cAMP- and G-protein receptor signaling. Thus, MER20 is argued to have been involved in the origination of placentation and pregnancy in placental mammals, by recruiting the cAMP-signaling pathway into endometrial cells.

Although TE recruitments may have led to the origination of pregnancy as discussed above, examples from the literature reveal that many placental TE co-options have also occurred more recently in mammalian history, suggesting that TEs have mediated the diversification of placental tissues in addition to their origination. This article reviews the data supporting the idea that TEs have promoted rapid evolution of tissues at the maternal–fetal interface and discusses the mechanisms by which these TE recruitments have occurred. First, we briefly summarize the variety of ways TEs have known to influence placental form and function. Second, we go into depth on two examples: (i) ERV-derived envelope genes expressed in fetal placental cells and (ii) retroelement-derived promoters for prolactin expression in the endometrium. Third, we introduce and describe a mode of molecular evolution by which TEs are transformed into host regulatory elements in placental and potentially other tissues, called epistatic capture. Epistatic capture is the process by which a transcription factor binding site (TFBS), which is present in a TE upon insertion but variable in outgroup lineages because it is not under constraint, becomes stabilized in a derived group by epistatic interactions with derived TFBSs. By this mode of evolution, pre-existing TFBSs, which are found frequently in TEs, are critical for the origin of a new activity in a tissue like the placenta. Finally, we discuss the potential role of TEs in the evolution of non-placental tissues.

How are TEs used by host tissues like the placenta?

There are a variety of ways TEs have impacted placental form and function in mammalian species (for more in-depth reviews, see Refs [6, 7]). Their greatest impact may be on gene regulation. By donating new promoters, enhancers and other cis-regulatory elements, they are able to recruit new genes into placental expression or change expression levels of genes already expressed. One of many examples involves pleiotropin, a growth factor expressed in the human trophoblast that uses a long terminal repeat (LTR) element from an ERV as a tissue-specific promoter [8]. Other examples include the leptin gene, which in humans is expressed in the placenta because of an LTR-derived enhancer [9] and INSL4, which uses...
an LTR-derived promoter for expression in the human placenta [10]. In many cases, TE-derived cis-regulatory elements are lineage specific (i.e., found in some species/clades but not in others), thus influencing gene expression in only a subset of placental mammals. This suggests that the potential for molecular innovation may dramatically differ between lineages, depending on the number and kind of TEs present and active in a particular lineage.

Another obvious way TEs influence placental form and function is by donating new genes that can be expressed in the placenta. TEs code for proteins that are essential for their own reproduction. Thus, through transposition, TEs distribute copies of protein-coding genes throughout the host genome. Envelope genes of ERVs, transposase genes of DNA transposons and reverse transcriptase and integrase genes of retroelements are the types of TE-derived genes that can be recruited into host expression [11]. For example, envelope protein genes of ERVs have been domesticated multiple times in placental mammals, which will be discussed in detail in the next section.

TEs can cause recombination events (often between lineage-specific Alu elements and LTRs), which can result in the duplication of genes. This might lead to new or altered gene functions. A good example is the growth hormone gene, which in catarrhine primates initially duplicated because of an Alu-mediated recombination event [12]. The duplicated growth hormone genes are expressed in the placenta and the hormones engage in novel interactions with growth hormone and prolactin receptors in placental tissues [13]. Thus, the Alu-mediated duplication has played a major role in the evolution of placental function in the higher primates [13].

Another way TEs might contribute to placental function is by recruiting gene-silencing machinery, which can turn off alleles of maternal or paternal origin and thus contribute to genomic imprinting. Many imprinted genes are expressed in the placenta and are involved in nutrient exchange between the mother and fetus [14, 15]. Imprinted genes and TEs exhibit similar epigenetic modifications (CpG methylation) and different TEs are epigenetically marked in male and female gametes differently (e.g., L1 elements are hypomethylated in eggs and SINE elements are hypomethylated in sperm) [16, 17]. Thus, it is possible that TEs mediate imprinting [18]. In fact, it has been argued that imprinting originated in therian mammals in response to the accumulation of certain LTRs and DNA elements in early therians [19]. Two examples of imprinted genes derived from retroelements are PEG10 and PEG11; knockout of these genes in mice results in fetal death, underscoring their importance in placental function [20, 21].

**Envelope genes of ERVs recruited in primates, glires and sheep**

A number of studies have investigated the role of envelope genes of ERVs expressed in the placenta. ERVs are a class of TE related to exogenous retroviruses, which use envelope proteins to fuse with and then infect the host cell. In many species, envelope genes of ERVs are expressed in trophoblast cells, cells of fetal origin that contribute to the placenta.

**Primates**

The first envelope genes characterized and shown to have a likely role in placental morphogenesis were discovered in primates. The two genes belong to the HERV-W and HERV-FRD ERVs and the former gene is found in apes and the latter in monkeys and apes. The genes were named syncytin-1 and syncytin-2 and they remain conserved structurally and functionally [22, 23]. Syncytin-1 and Syncytin-2 are expressed almost exclusively in the placenta, in cytotrophoblast and syncytiotrophoblast cells. In vitro transient transfection assays showed that both genes can trigger cell–cell fusion in mammalian cells [24] and that syncytin-1 induces trophoblast differentiation and fusion [25]. Additional work revealed that syncytin-1 is also expressed in invading extravillous trophoblast cells [26], which in apes are responsible for deep invasion of fetal tissues, and that syncytin-2 has immunosuppressive activity [27].

**Glires (rodents and relatives)**

Genome-wide searches in mice revealed that mice also contain two fully coding envelope genes that are expressed in the placenta, but they are not homologous to those in primates [28]. These genes, named syncytin-A and syncytin-B, have orthologues in various murine rodents, suggesting that they integrated in the rodent lineage about 20 million years ago. Syncytin-A and Syncytin-B are expressed almost exclusively in the placenta, specifically in syncytiotrophoblast layers. Like their primate counterparts, the genes were shown to trigger cell–cell fusion in vitro [28]. Knockout of syncytin-A confirmed that it is
required for placental form and function: there was deficient cell–cell fusion in the syncytiotrophoblast layer of the placenta of knockout mice, resulting in impaired nutrient exchange at the maternal–fetal interface and fetal death [29].

Non-murine rodents (e.g. guinea pigs) and other members of the rodent–lagomorph clade (e.g. rabbits), which lack syncytin-A and syncytin-B, also form a syncytium. Thus, they must have another way of inducing fusion between trophoblast cells. A major difference between murine and non-murine rodents is that murine rodents have two syncytiotrophoblast layers as opposed to one and it has been hypothesized that co-option of syncytin-A and syncytin-B contributed to this difference [28]. A recent report on envelope genes in rabbits demonstrated that they express a non-orthologous envelope gene, called syncytin-Ory1, that has fusogenic functions like the syncytin genes in primates and rodents [30]. Also, a recent report on envelope genes in the guinea pig placenta showed that syncytin-like enw-Cav1, a gene only found in guinea pigs and other members of the Caviidae family (i.e. not in rodents or rabbits), is expressed in the placenta, but at the level of the invasive trophoblast, not of the syncytiotrophoblast [31]. The gene does not promote cell–cell fusion in vitro, but is thought to have a role in trophoblast invasion, as has been suggested for syncytin-1 in primates.

**Sheep**

Remarkably, it was also reported that the envelope of one family of ERVs in sheep, called enJSRV, is involved in placental morphogenesis in the sheep. Dunlap et al. [32] showed that the envelope of enJSRVs is expressed in the ovine trophoblast after day 12 of pregnancy. Using an *in utero* knockdown approach, with a morpholino designed to inhibit translation of most enJSRV loci, they showed that enJSRV envelope is essential for fetus elongation and trophoblast cell differentiation during the peri-implantation period [32]. Pregnancy loss occurred by day 20 of pregnancy as a result of the knock down, showing that the protein is required for successful pregnancy. *In vitro* experiments confirmed that the envelope of enJSRV is involved in growth and differentiation of trophoblast, but it did not promote cell–cell fusion.

The cases described above highlight how frequently envelope genes have been co-opted for important host functions in the mammalian placenta. It appears that in addition to the independent co-option of these genes for fusogenic functions in primates, murine rodents and rabbits, they might also have been co-opted for invasive, immunosuppressive and other roles in the primate, guinea pig and sheep placenta. The domestication of different envelope genes for convergent and divergent functions in fetal tissues across species supports the idea that diversification of the placenta has been mediated, at least in part, by the co-option of TEs in placental tissues.

**Retroelement-derived promoters for endometrial prolactin expression in primates, rodents and elephants**

Placentation is a complex process involving communication between maternal and fetal tissues. The deciduial endometrium, the site of attachment of the fetal placenta, plays critical roles in fetal attachment and restraint, the maternal immune response and hemostasis. There is evidence suggesting that the relationship between tissues at the maternal–fetal interface is antagonistic, since the mother and fetus do not carry identical sets of genes and thus do not have the same evolutionary interests [14, 15]. Maternal–fetal conflict, in fact, is thought to be the driving force underlying such fast evolution of tissues at the maternal–fetal interface [14, 15]. Given the intimate and conflicting relationship between fetal tissues and the endometrium during pregnancy, diversification of the placenta involved evolution of both maternal and fetal tissues that contribute to this organ. If indeed co-option of TEs facilitated diversification of fetal components of the placenta as reviewed above, we might expect a similar situation on the maternal side, i.e. the endometrium.

It was recently shown that prolactin expression in the endometrium has evolved at least three times in the history of eutherian mammals, in each case by the co-option of a different TE for a novel alternative promoter [33, 34]. Endometrial prolactin is a signaling molecule thought to be involved in a variety of functions during pregnancy, including angiogenesis, communication with fetal tissues, communication with the maternal immune system and the maintenance of pregnancy [35]. It is one of the most strongly upregulated genes in the human endometrium during pregnancy and one of the most abundant secretory products in the amniotic fluid. In addition, prolactin knockout mice are infertile, even when administered progesterone [36].
These mice have elevated endometrial levels of Il-6 and 20kHSD, two proteins detrimental to the maintenance of pregnancy [36]. These genes are not expressed in the decidua of wild-type mice and their expression is inhibited by prolactin treatment, suggesting that prolactin action in the decidua is necessary for successful pregnancy [36]. (Note that rodents have a large family of prolactin paralogues; the knockout mentioned is of the rodent parologue orthologous to the prolactin gene in humans and other mammals) [36].

The human promoter for endometrial prolactin expression derives from a lineage-specific LTR element called MER39 [37]. The MER39-derived promoter, located about 6 kb upstream of the coding region of the gene, is alternative to that which drives expression in the pituitary. By testing pregnant endometrial tissue from a variety of placental mammals, it was found that decidual prolactin (dPrl) expression is not a shared character of all placental mammals: it is expressed in the higher primates, rodents and elephant, but has not been found in rabbits, dogs, pigs or armadillos [33]. Moreover, it was discovered that in the groups in which dPrl is expressed, the mechanisms of expression are different. The MER39-derived promoter is conserved in the higher primates, as transcription of the gene in spider monkey initiates in MER39. However, mice initiate transcription in a completely different genomic location, about 53 kb upstream of the coding region, in a different LTR element called MER77. Remarkably, transcription in the elephant initiates in yet another TE, in this case a lineage-specific LINE element called L1-2_LA. Thus, Prl was independently recruited at least three times into endometrial expression by the co-option of different retroelements, a situation similar to that of the envelope genes described above. In this case, however, the TEs were recruited for cis-regulatory function.

It is unclear what the precise function(s) of decidual prolactin are in the groups in which expression of the gene evolved. It is notable, however, that all three groups shown to express dPrl during pregnancy—the higher primates, rodents and the elephant—experienced accelerated evolution of the prolactin protein. Wallis [38] showed that four lineages in eutherian mammals underwent accelerated Prl coding sequence evolution: the lineages giving rise to the higher primates, rodents, the elephant and ruminant artiodactyls (which were not tested for dPrl expression in Ref. [33]).

The correlation between dPrl expression and accelerated Prl evolution suggests that the selective forces that drove Prl sequence evolution were in the endometrium [33]. In addition, it supports the idea that dPrl expression, which evolved via TE co-options, is adaptively important for the groups in which it evolved [33].

**Mechanisms of TE recruitments as cis-regulatory elements**

The examples above highlight how frequently TEs have been recruited in placental tissues and suggest that they have had a major impact on the diversification of this organ in mammals. What are the mechanisms by which TEs are recruited for functions in the placenta? Are they used immediately upon insertion at a genomic locus or do they require modification before acquiring a biological role for the host? Additional work on TEs at the Prl locus helps to answer these questions, at least for the recruitment of TEs for regulatory functions. First, it is clear that MER39 and MER77, the LTR elements co-opted for dPrl expression in primates and mice, respectively, required substitutions to the elements before acquiring a biological role for the host. One line of evidence is that all primates and glires have both MER39 and MER77 at the Prl locus, but only the higher primates use MER39 and mice MER77 for Prl expression in the endometrium [33]. Also, rabbits have both elements, but Prl expression has not been found in the endometrium during pregnancy. Additional evidence comes from experiments showing that tarsiers, which are basal primates, do not use MER39 as a promoter [34]. This all suggests that after insertion at the Prl locus, MER39 and MER77 had no impact on Prl expression in the endometrium and were domesticated later, after the sequences accumulated the necessary substitutions.

There are other examples suggesting that TEs require substitutions before acquiring a biological role for the host [39]. One study analysed two human HERV-E LTR elements that contribute to expression of the endothelin-B receptor gene (EDNRB) and the apolipoprotein C1 gene (APOC1) [40]. The LTR elements are 85% identical in humans, but the EDNRB LTR is a very strong promoter in the placenta, whereas that driving expression of APOC1 is a weak promoter in all tissues studies including the placenta. One region in the EDNRB LTR (called LPE2), which is necessary for
driving strong expression in the placenta and contains three putative TFBSs, differs by a number of bases from the \textit{APOC1} LTR and other LTR elements analysed. Thus, derived TFBSs in the \textit{EDNRB} LTR were involved in conferring strong placenta-specific expression of the gene. A similar situation has been described for an Alu element that acts as an enhancer for the CD8 gene expressed in human T-cells. Two characterized TFBSs in the Alu element near CD8 differ from the consensus Alu sequence in a number of positions and are necessary for T-cell-specific activity; thus, the Alu element underwent important substitutions before acquiring a biological role for the host [41]. An Alu-derived promoter driving expression of the interferon-\(\gamma\) gene in human lymphocytes also underwent a series of substitutions that created an NF-\(\kappa B\) site necessary for activity of the \textit{cis}-regulatory element [42].

There are two thoughts on why TEs, like those discussed above, might be such a good source of \textit{cis}-regulatory material [1]. First, since many TEs (especially retroelements) need regulatory elements to control their own transcription and transposition, it is possible that TEs provide these same regulatory elements to the host ‘ready-made’ upon insertion. LTR elements, for example, contain a variety of transcription regulating signals [43]. Second, decaying TE sequences might simply provide raw genetic material, mutationally close to many TFBS sequences, from which \textit{cis}-regulatory elements can emerge \textit{de novo}. The work discussed above suggests that some TFBSs emerge \textit{de novo} from decaying TE sequences. However, a close investigation of the recruitment of MER39 for \(P\text{rl}\) expression in primates reveals a more complex mechanism.

As mentioned above, MER39 was not a promoter for \(d\text{Prl}\) upon insertion. It evolved to be a weak promoter in monkeys and then it became a very strong promoter in apes [34]. However, one binding site necessary for strong promoter activity in apes, that for the transcription factor ETS1, was present in MER39 upon insertion at the \(P\text{rl}\) locus [34]. The ETS1 site is variably present in non-apes with MER39, but is conserved in the apes. In addition, it appears that interactions between the ETS1 site and a handful of ape-derived sites in MER39 are required for strong promoter activity in apes. In fact, it has been suggested that stabilization of the ETS1 site in apes occurred because of new interactions with the ape-derived sites. The new interactions resulted in increased \(d\text{Prl}\) expression in stem apes and may have been an adaptive maternal response to highly invasive ape placentation [34]. This mode of molecular evolution has been called epistatic capture [34]. Epistatic capture is the process by which a TFBS comes under increased purifying selection due to epistatic interactions with derived TFBSs. Thus, a TFBS that is present in a TE upon insertion but under no constraint in outgroup lineages, becomes stabilized in the ingroup as a result of the new interactions with derived sites (Figure 3) [34].

Epistatic capture might be a general mode of molecular evolution [44], but it is likely relevant for TEs and retroelements in particular since they contain a variety of regulatory signals to begin with for their own transposition. In the \textit{EDNRB} case described above, for example, another region in the LTR close to LPE2 (called LPE1, with a hypothesized SP1 site) is necessary for strong promoter activity. LPE1 is ancestral to the TE, as other LTR elements including that near the \textit{APOC1} gene have LPE1 conserved. Also, the Alu element driving expression of the CD8 gene uses an ancestral TFBS in addition to some derived TFBSs mentioned above. Thus, it appears that many TEs with \textit{cis}-regulatory activity are active in a host tissue because of a combination of ancestral and derived TFBSs. To our knowledge, interactions between ancestral and derived TFBSs have only been documented in MER39, but given the proximity of these sites in the examples above, these interactions probably also occur in other TEs.

\textbf{Figure 3:} Model of ‘epistatic’ capture, a mode of molecular evolution by which TEs are recruited for tissue-specific functions. (A) TE insertion, with ancestral transcription factor binding site, at new locus; (B) nearby substitutions to primordial binding sites for tissue-specific transcription factors; (C) ‘Epistatic capture’ and origin of tissue-specific \textit{cis}-regulatory activity.
Epistatic capture may not be the only mechanism by which TEs are co-opted, as there are known cases of TEs having many of the TFBSs required for host regulatory activity upon insertion [45]. However, it is not a surprise that at least some TEs require modification after insertion to be used by the host. Retroelements must be active in the male and female germlines in order for transpositions to be vertically transmitted. Thus, the LTRs and regulatory regions of successful retroelements need to be responsive to the trans-factors present in the germline. Tissues like the placenta are not expected to have the exact same transcription factor profile as the male or female germline. Thus, many TEs may require modification to an existing regulatory region before being recruited by non-germline tissues.

CONCLUSIONS AND FUTURE DIRECTIONS

A preponderance of evidence indicates that TEs have been recruited frequently for functions during pregnancy and have influenced the evolution of tissues at the maternal–fetal interface. Using two in-depth examples for illustration—the envelope genes of ERVs co-opted in fetal placental tissues and the retroelement-derived promoters for decidual prolactin expression in the endometrium—this article argues that the independent domestication of TEs in different groups of placental mammals for functions both convergent and divergent strongly supports the idea that TEs have facilitated the diversification of placental tissues. Differences in the complement of TEs in different lineages may also contribute to lineage-specific potential for diversification and innovation. This article also discusses the mechanisms by which TEs are co-opted for regulatory functions in placental tissues. It appears that many TEs use a combination of ancestral TFBSs and derived sites to drive placenta-specific expression of a host gene and were transformed into functional regulatory elements by epistatic capture. Thus, TEs provide a good substrate from which cis-regulatory elements can evolve, but they do require some modification before being recruited by a host tissue such as the placenta.

Many of the examples discussed here describe co-option in the placenta of LTR-containing TEs. In fact, in a review on host recruitment of LTR elements for promoter functions, Cohen et al. [46] claim that LTR co-options have rarely led to novel expression patterns except in the placenta. It is unknown if and why this correlation exists. It is possible that LTR elements are ‘pre-adapted’ for use in the placenta, i.e. their sequences are closer to containing the optimum TFBS profile for placental tissues than other TEs. Alternatively, it has been shown that the genome of fetal placental cells is hypomethylated relative to other tissues [47, 48]. Therefore, TEs may be less epigenetically silenced in the placenta and more likely to impact regulation of nearby genes. However, if this were true, we would expect all classes of TEs to be used more frequently in the placenta than in other tissues, which has not been shown. To help clarify this issue, it will be useful to investigate if a correlation exists between other classes of TEs—such as non-LTR retroelements and DNA transposons—and activity in the placenta versus other tissues.

Future work might also explore the role of TEs in the evolution of other rapidly evolving tissues. A variety of molecular mechanisms likely underlie the rapid, lineage-specific evolution of a tissue like the placenta. These mechanisms include accelerated coding-region evolution of genes expressed, fast evolution of gene expression and the expression of new genes [49]. As mentioned in this article, TEs may be involved in many of these molecular mechanisms: TEs have donated new genes that are expressed in the placenta to some lineages (e.g. the env gene of ERVs), they have promoted genomic rearrangements that resulted in the duplication of genes expressed in the placenta (e.g. the Alu-mediated growth hormone duplication in primates) and they have affected evolution of gene expression in the placenta (many examples, including the case of Prl). It has even been noted that genes with rapidly evolving coding regions are more likely to intersect with TEs in their regulatory regions [50]. Thus, TEs have been involved in placental evolution at many mechanistic levels. This may be true of other highly diverse tissues like the testes, which are thought to evolve quickly because of sperm competition [51–53]. To further explore this hypothesis, the role of TEs in testes evolution should be explored. This kind of investigation will complement the work reported on here and will give us a more comprehensive understanding of the role of TEs in phenotypic evolution.
Transposable element recruitments

Key Points

- TEs are increasingly recognized as important players in the evolution of genome structure and function.
- The frequent and independent recruitment of TEs in different mammalian lineages for functions in the placenta supports the idea that they have facilitated the diversification of this organ.
- TEs can be recruited for tissue-specific functions by a mode of molecular evolution called epistatic capture.

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References