Endogenous Retroviruses in Domestic Animals

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Abstract: Endogenous retroviruses (ERVs) are genomic elements that are present in a wide range of vertebrates. Although the study of ERVs has been carried out mainly in humans and model organisms, recently, domestic animals have become important, and some species have begun to be analyzed to gain further insight into ERVs. Due to the availability of complete genomes and the development of new computer tools, ERVs can now be analyzed from a genome-wide viewpoint. In addition, more experimental work is being carried out to analyze the distribution, expression and interplay of ERVs within a host genome. Cats, cattle, chicken, dogs, horses, pigs and sheep have been scrutinized in this manner, all of which are interesting species in health and economic terms. Furthermore, several studies have noted differences in the number of endogenous retroviruses and in the variability of these elements among different breeds, as well as their expression in different tissues and the effects of their locations, which, in some cases, are near genes. These findings suggest a complex, intriguing relationship between ERVs and host genomes. In this review, we summarize the most important *in silico* and experimental findings, discuss their implications and attempt to predict future directions for the study of these genomic elements.

INTRODUCTION

Endogenous retroviruses (ERVs) are genomic elements that are present in a wide range of vertebrates, from basal vertebrates, such as sharks and rays, to mammals [1]. During the course of evolution, exogenous retroviruses have inserted themselves into the germ line, resulting in stably integrated endogenous retroviruses that are transmitted vertically to offspring [1].

ERVs contain three main genes: *gag*, which encodes the proteins of the capsid; *pro-pol*, which encodes the enzymes for maturation, replication and insertion; and *env*, which encodes the envelope protein [1]. These genes are flanked by long terminal repeats (LTRs), which are control regions containing promoters, enhancers and polyadenylation signals [1]. In addition, other accessory genes could be present, such as the *trans*-acting regulatory proteins *tat* and *rev* [1].

ERVs comprise three different classes depending on their relationship with their exogenous counterparts [1]: Class I is related to *Epsilonretrovirus* and *Gammaretrovirus*; Class II to *Alpharetrovirus*, *Betaretrovirus*, *Deltaretrovirus* and *Lentivirus;* and Class III to *Spumavirus.*

Interest in these genomic elements has accumulated due to their possible involvement in diseases such as multiple sclerosis and cancer [2-4] or their impact in the evolution of the host genome, by means of change of nearby gene expression for example [5, 6]. The implications of ERVs presence in host genomes have been revised in [4, 7]. The presence of ERVs has been studied in some domestic animals since the late 1990s by Southern blot [8, 9] and PCR [9] analyses. In these studies, retroviral presence was detected in pigs, horses, sheep, goat, cattle, yak and cats [8, 9]. However, the in-depth study of ERVs has traditionally been limited to humans [10] and murids [11]. Fortunately, during the last years, more domestic species are being analyzed, and thus, we are gaining insight into ERVs in these species.

PRESENCE OF ERVs IN DOMESTIC ANIMALS

In the genomic era, when a genome is sequenced, the repeated elements are characterized using Repeatmasker or similar tools. The main characteristics of the sequenced genomes are shown in (Table **1**).

ERVs in domestic animals have been analyzed more in-depth using both experimental procedures (such as the amplification of retroviral sequences) and computational tools that were developed for this task (such as the LTR_STRUC [19], Retrotector© [20] or LTRharvest [21] programs). Recently they have been analyzed altogether with the rest of vertebrates to gain insight into the host-retrovirus evolution [22].

Moreover, a specific ERV can be present in all individuals of a population (fixed ERV) or it can be present in some individuals while in the rest of the population is not present. In this case it is considered a polymorphic ERV. The present knowledge on ERVs will be reviewed species by species.

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Table 1.   **Data from genome sequencing projects. WGS, whole genome sequencing; NGS, next generation sequencing.**

Species	Coverage	Method	Refseq mRNAs[a]	LTR/ERV[b]	
				Copies	Coverage[a]
Sus scrofa [c]	-	BAC / WGS	1.22%	-	4.48%
Canis familiaris [d]	7.5X	WGS	0.09%	306,000	3.87%
Felis catus [e]	1.9X-14X	WGS / NGS	0.09%	-	4.44%
Equus caballus [f]	6.8X	BAC / WGS	0.80%	-	6.19%
Ovis aries	-			-	
Capra hircus [g]	12X-65X	NGS / optical mapping	0.25%	561,426	4.66%
Bos taurus [h]	7.2X	BAC / WGS	0.86%	277,632	3.20%
Gallus gallus [i]	6.6X	BAC / WGS	2.41%	12,000	1.3%

[a] % of genome; [b] estimated by Repeatmasker; [c][12]; [d][13]; [e][14]; [f][15]; [g][16]; [h][17]; [i][18].

Pigs

ERVs of pigs (*Sus scrofa*) have been widely and deeply analyzed due to their ability to infect human cells, which is a barrier to xenotransplantation, since immunosuppressed patients could be more sensible to an infection by porcine ERVs [23]. The infectious porcine ERVs belong to Class I (members of PERV γ 1) and are classified into three subgroups depending on their *env* gene: PERV-A, -B and –C [24]. In addition, 4 non-infectious groups of Class I (PERV γ 2 to γ 5) and 4 groups of Class II (PERV β 1 to β 4) are also present in the porcine genome [24]. Most non-infectious PERVs have been detected in 5 species that are related to pigs (Bornean bearded pig, warthog, red river hog, chacoan peccary and collared peccary); thus, it seems that these viruses were inserted into a common ancestor of *Suidae* [24]. However, the presence of PERV *env* subgroups is more variable among different pig breeds and species that are related to pigs [24-27]; therefore, their origin appears to be more recent. It has been estimated that PERV γ 1 originated approximately 7.5 MYA, although the PERV-C subtype could have been inserted between 1.5-3.5 MYA [25]. Finally, a copy of PERV γ 2 was inserted between 0.1-0.2 MYA [28].

Recently, PERV γ 1 and PERV γ 2 have been more thoroughly analyzed to infer their evolutionary history [26]. The genes *gag* and *pol* and the four *env* subtypes (PERV-A, PERV-B and PERV-C; and PERV-E, which is a PERV γ 2) were used to infer the relationships between PERVs in pigs and 10 related species [26]. Based on the phylogenetic analyses of these genes, two lineages of PERV γ 1 were detected: one from Eurasian species and the other from African species [26]. However, PERV γ 2 did not show a clear differentiation between species [26] because it was previously described for 6 pig breeds [28].

In another study, the variability of PERV γ 1 among different pig breeds was also analyzed [29]. The number of copies of the PERV γ 1 *pol* gene appeared to be variable among 2 breeds, 2 wild boars and 5 commercial cross-bred pigs [29]. Furthermore, the number of copies did not correlate with the heterozygosity of the population or individuals, or with the inbreeding coefficient of populations [29].

Regarding PERV γ 2, 6 breeds were analyzed to detect the presence of the *pro/pol* complex [28]. The number of copies was variable among breeds, and the number of intact PERV γ 2 appeared to be low [28].

Finally, in an *in silico* screening of the pig genome using LTRharvest, 156 elements were detected [30]. Most of these elements belonged to the PERV γ 1, PERV γ 2 and PERV β 3 families, but elements of a new family, termed ERV1N-2, have also been described [30]. Moreover, in a screening using Retrotector© 551 elements were detected [12]. Most of them belonged to Class I ERVs and Class II was the second more represented class [12].

Dogs

The analysis of ERVs in dogs (*Canis familiaris*) has been carried out by different experimental and *in silico* methods, especially after the publication of the canine genome in 2005 [13]. In a genome-wide analysis using Retrotector©, 407 proviruses were detected [31]. These ERVs composed 0.15% of the canine genome, and they had an average length of 9 kb [31]. The most abundant elements were from Class I, while elements from Class II and Class III were more scarce [31]. The insertion time of these elements was estimated to be approximately 12.5-25 MYA [31]. These ERVs were mainly located in intergenic regions, and the presence of ERVs was correlated with chromosome length and the numbers of coding genes and non-coding RNAs [31]. Due to the under-annotation of dog genes, only a few genes (7 in total) appeared to be located near ERVs (up to 5 kb). However, using a homology-based approach to analyze regions where canine ERVs appeared in comparison to their human homologs, up to 211 genes seemed to be related to ERVs [31].

In a more recent work based on the use of degenerative PCR of the *pro-pol* complex and BLAST searches, more ERVs were discovered in the canine genome [32]. In this experimental approach, 81 unique sequences were detected, all of which belonged to Class I ERVs, and they were classified into 4 groups: CfERV γ 1 to γ 4 [32]. The number of sequences that clustered in each group and their lengths were variable [32], with CfERV γ 1 being the most abundant (48

sequences clustered in this group), and sequences from CfERV γ 2 being slightly shorter. These sequences and retroviral sequences of other species were used to carry out an *in silico* analysis using BLAST against the canine genome. On the whole, 168 sequences were identified as ERVs: 160 from Class I and 8 from Class II [32]. The elements from Class I clustered into 17 subgroups (CfERV γ 1 to γ 17), while the elements from Class II clustered into 7 groups (CfERV β 1 to β 7) [32]. However, some concerns have been raised regarding this classification [33]. Their insertion could have occurred between 2.35-25.63 MYA according to conservative estimates, or, if the criteria were relaxed, it could have occurred between 0.83-42.97 MYA [32]. An additional BLAST search was performed for ERVs from Class III using sequences from human and mice ERVs, and 167 elements were detected in the canine genome [32].

A final study analyzed the relationship and presence of ERVs between different dog breeds: 7 loci of canine ERVs were amplified in 20 different breeds, and all of the ERVs were found to cluster into Class I; thus, they could be a monophyletic group in *Canidae*. Their insertion could have occurred between 12-22 MYA [33].

Cats

Until recently, the lack of genomic information of cats (*Felis catus*) has prevented genome-wide analyses of ERVs. However, some studies on specific feline ERVs have been performed.

In a study on the endogenous form of feline leukemia virus (enFeLV), which is a *Gammaretrovirus*, domestic and wild cats were analyzed to detect env-LTR and LTR sequences of enFeLVs [34]. No evident differences in the presence of enFeLVs were observed between domestic cat and its similar wild relatives [34]. In addition, the sequences of enFeLVs from the domestic cat and its nearest wildcat species (*F. silvestris* and *F. lybica*) clustered together; therefore, it seems that these copies were present before cat domestication and that there has not been any substantial activity since then [34].

Another group of feline ERVs called ERV-DC is not yet fixed; therefore, they can generate recombinant retroviruses that could be infectious [35]. Ten full-length ERV-DC copies have been detected, and 4 have intact *gag*, *pol* and *env* genes [35]. Furthermore, the presence of members from the ERV-DC group was variable among 244 analyzed cats, which had between 7 and 17 copies, and the insertion occurred 2.8 MYA [35]. Of the ERVs of this group, 2 (named ERV-DC10 and ERV-CD18) are infectious and are currently being transmitted [35].

Recently, a genome-wide search of ERVs in the cat genome using degenerative PCR of the *pro-pol* complex and BLAST searches was carried out, and 219 ERVs were detected [36]. In an approach using degenerate PCR, 9 families of class I (FcERV γ 1 to γ 9) and 1 family of class II (FcERV β 1) were identified. In *in silico* analysis, where the *Felis catus*-6.2 assembly was analyzed, 33 more families of class I (FcERV γ 10 to γ 42) and 3 more families of class II (FcERV β 2 to β 4) were identified, although 24 of those families comprised one or two members [36]. Of the de-

tected ERVs, 51 were full-length retroviruses with a complete structure [36]. In addition, 757 putative ERVs from Class III were detected, but their classification into families was difficult [36]. The most abundant families were γ 6 (35 members) and γ 1 (18 members), and their integration times were estimated to be 3.8-16 MYA and 8.2-30 MYA, respectively. On the whole, the feline ERVs were inserted between 2.3 and 41.7 MYA [36].

Horses

The horse (*Equus caballus*) genome was released in 2009 [15], and since then, different *in silico* studies have been performed to detect equine ERVs in a genome-wide manner. In an initial study to characterize equine ERVs, a computational search of retroviral genes was carried out using BLAST and BLAT tools against the horse genome [37]. However, of the detected genes, those that belonged to Class I were fragmented, although, interestingly, one of the proviruses from Class II was a complete provirus (named EqERV-beta1) [37].

In another approach, exonerate algorithms were used to detect retroviral genes, and LTRharvest was used to find LTR pairs [38]. In this analysis, 978 sequences were annotated as potential ERVs that belonged to Class I and Class II retroviruses [38].

In a final study, BLAST, LTR_STRUC and Retrotector© were used to detect ERVs in the equine genome [39]. In this approach, 1947 putative ERVs were detected, but only 310 were tested by additional methods [39]. Those ERVs belonged to the three previously mentioned retroviral classes, and some were classified into 15 families or groups: 9 families from Class I, named EqERV1 to EqERV9; 4 from Class II, named EqERV12 to EqERV15; and 2 from Class III, named EqERV10 and EqERV11 [39]. It seems that the oldest element could have been inserted between 68-148 MYA, and the youngest could have been inserted between 0-1 MYA [39].

Sheep

Sheep (*Ovis aries*) have been used as models of coevolution between a host and ERVs, in particular, the Jaagsiekte Sheep Retrovirus (JSRV) and its endogenous counterpart, enJSRV, because both forms are still active and strongly interact [40]. Actually, enJSRVs appear to block JSRV at two levels. The first block acts at the level of virus entry by receptor interference, while the second step most likely blocks viral particle transport or exit [41-43].

A previous study provided a nice example for the usefulness of ERVs as genetic markers, in which enJSRVs were used to examine the history of different sheep breeds [44]. Although most enJSRV loci are fixed in domestic sheep, some are differentially distributed between breeds and individuals (i.e., they are insertionally polymorphic). The presence of 6 polymorphic enJSRV copies (enJSRV-18, enJSRV-7, enJSRV-8, enJSRV-15, enJSRV-16 and enJS5F16) was examined in 133 sheep breeds, Urial sheep and Mouflons [44]. The percentage of each provirus was variable among different populations (e.g., enJSRV-18 was highly frequent in the Old World) and this variable was used

to define "retrotypes" [44]. The retrotypes R2 (presence of enJSRV-18) and R4 (presence of enJSRV-18 and enJSRV-7) were the most common, and on the whole, different retrotypes were associated with the expansion and selection of desired features in modern sheep breeds [44].

For the rest of the ERVs present in the sheep genome, 9 families from Class I (OERV $\gamma 1$ to $\gamma 9$) and 3 families from Class II (OERV $\beta 1$ to $\beta 3$) have been described based on amplification of their *pro/pol* complex [45].

Cattle

The cow (*Bos taurus*) genome has traditionally been analyzed by experimental procedures, but after the release of the cattle genome [17], many *in silico* analyses have been performed to detect ERVs. Using degenerate PCR of the *pro/pol* complex, sequences of 3 retroviral families of Class I (BERV $\gamma 4$, $\gamma 7$ and $\gamma 9$) and 1 family of Class II (BERV $\beta 3$) were detected in cattle and were named depending on their relationship with ovine ERVs [46]. The most abundant family was BERV $\gamma 4$, while BERV $\gamma 7$ and $\gamma 9$ were more scarce [46]. Some of these ERV families have been studied more in depth. In the BERV $\gamma 4$ family, for example, a complete provirus was identified that has been demonstrated to be distantly related to *Gammaretroviruses* [47]. However, the most conserved provirus in BERV $\beta 3$ has several stop codons and is closely related to the HERV-K human family [48].

A genome-wide detection of ERVs in the cow genome was carried out using three computational tools (BLAST, LTR_STRUC and Retrotector©) [49]. In total, 13,622 putative ERVs were detected, although only 1,532 were tested by an additional two or three programs [49]. Some of these ERVs could be classified into families: 18 families from Class I and 6 from Class II, but no ERV belonging to Class III was detected [49]. In this study, the previously known 4 families were also detected; thus, 20 new families were discovered in the genome-wide analysis [49]. The oldest element could have been inserted between 58-126 MYA, and the youngest seems to be a recent integration event [49]. Of these families, the one termed BoERV1 was the most abundant and appeared to be specific to ruminants [49]. In a newer genome version of the cattle genome using Retrotector©, a similar number of ERVs were detected [50]. Finally, cattle genome was reexamined using LTRharvest and LTRdigest and 6 additional families of bovine ERVs were detected: BoERV25-BoERV27 from Class I and BoERV28-BoERV30 from Class II [51].

Unfortunately, as far as we know, knowledge on the variability of ERVs in cow breeds is limited to ERVs that are similar to ovine enJSRV [52]. For example, ERVs that are closely related to enJSRVs were detected in Simmental and Limousine breeds [52], but they were not detected in the reference cattle genome (a Hereford cow) [49]. Finally, expression of the *env* gene of these enJSRV-like elements was also detected and was limited to the bone marrow [52].

Chickens

Of the domestic animals reviewed here, the chicken (*Gallus gallus*) is the only non-mammal species. After the se-

quencing of the chicken genome, 3 groups of chicken ERVs were defined: the ev loci, which is related to Avian Leukemia Virus (ALV); the EAV family; and sequences related to the human HERV-I ERV family [53]. However, the EAV family seemed to belong to the same family as that which contained the Avian Leukemia Virus [53].

Using an experimental approach, a full-length ERV, termed ChiRV1, was also detected in the chicken genome [54]. Nevertheless, this ERV was not intact and contained some stop codons [54]. Furthermore, ChiRV1 belonged to Class I and was related to the Murine Leukemia Virus [54]. The chicken genome possesses approximately 100 sequences related to this ERV, but most are solo-LTRs, that is, the remains of complete ERVs which contains the LTR detached from the rest of the ERV sequence (that have been deleted by homologous recombination between the LTRs) [54].

The OVEX1 chicken ERV was found by searching for genes related to ovarian differentiation [55]. This element is distantly related to Class III ERVs and is a full-length ERV [55]. In addition, in a genome-wide approach using the LTR_STRUC program, 39 putative full-length ERVs were detected [56]. Using the reverse transcriptase region of these ERVs, 14 ERV families were described, and the families GGERV21, GGERV22 and GGERV30 were revealed to be the most abundant [56].

In another genome-wide analysis, 492 ERVs were detected using Retrotector© [57]. These ERVs belonged to the 3 retroviral classes, and the most abundant were from Class I and II [57]. Approximately 25% of them were inserted within or near genes, and most of them were found in introns [57].

The most important findings in the seven reviewed species are summarized in (Table **2**).

EXPRESSION OF ERVs IN DOMESTIC ANIMALS

The expression of ERVs has been analyzed in different tissues and organs by different methods such as RT-qPCR and RNA-Seq.

Pigs

Because the pig appears to be a promising animal donor of organs for use in human recipients, the main concern regarding PERVs is their ability to infect human cells. Thus, PERV expression has been widely analyzed. In a recent study on miniature pigs, RT-qPCR, Western blot and immunohistochemistry were used to detect the expression of PERV $\gamma 1$ sequences [58]. High expression of PERVs was detected in the lungs, spleen and lymph nodes, while low expression was found in the cerebrum, myocardium, muscle, colon and kidney [58]. However, proviruses from PERV $\gamma 2$ did not show a consistent pattern [28]. RT-qPCR has also been used to detect the expression of the *pro/pol* complex in 8 tissues (blood, heart, kidney, liver, lung, placenta, spleen and thymus) of pregnant sows of the same breed and their fetuses, but the detection of *pro/pol* was variable [28]. Thus, PERV $\gamma 2$ is not likely a risk for xenotransplants due to their partial expression of defective copies of ERVs [28]. For the remaining PERV groups (PERV $\gamma 3$ to $\gamma 5$ and $\beta 1$ to $\beta 4$), no expression patterns have been detected [24].

Table 2. Methods used to detect ERVs in domestic animals and their results.

Species	Methods		Families or groups			Complete ERVs	Polymorphic ERVs
	Experimental	*In silico*	I	II	III		
Sus scrofa	PCR [a]	LTRharvest, Retrotector©[b]	PERV γ 1 to γ 5	PERV β 1 to β 4	NA	NA	NA
Canis familiaris	PCR [c]	Retrotector© [d]	CfERV γ 1 to γ 17	CfERV β 1 to β 7	Yes	17/44	NA
Felis catus	PCR [e]	BLAST [f]	FcERV γ 1 to γ 42	FcERV β 1 to β 4	Yes	51	Yes
Equus caballus		BLAST, BLAT [g], Exonerate, LTRharvest [h], LTR_STRUC, Retrotector© [i]	EqERV1 to EqERV9	EqERV12 to EqERV15	EqERV10 to EqERV11	1/809	NA
Ovis aries	PCR [j]		OERV γ 1 to γ 9	OERV β 1 to β 3	NA	NA	Yes
Bos taurus	PCR [k]	BLAST, LTR_STRUC, Retrotector©, LTRharvest[l]	BoERV1-BoERV18, BoERV25-BoERV27	BoERV19-BoERV24, BoERV28-BoERV30	No	7180	NA
Gallus gallus	PCR [m]	LTR_STRUC [n], Retrotector© [o]	Yes	Yes	Yes	3	Yes

NA, not analyzed. If it is defined, the names of families or groups are showed.

[a] [24]; [b] [12, 30]; [c] [32, 33]; [d] [31]; [e] [34–36]; [f] [36]; [g] [37]; [h] [38]; [i] [39]; [j] [45]; [k] [46–48]; [l] [49, 51]; [m] [53–55]; [n] [56]; [o] [57].

In another RT-qPCR analysis, high expression of the PERV γ 1 family in an epithelial kidney cell line and moderate expression in embryonic germ cells and neonatal fibroblasts were found. However, the expression of PERV γ 2 and PERV β 3 was limited [30]. Based on DNA methylation and histone deacetylation analyses, the repression of expression was shown to be family specific [30]. It has been demonstrated that DNA methylation is involved in the regulation of most PERV-A and -C subgroups and that only a minor fraction of proviruses are responsible for PERV RNA expression and porcine cell infectivity [59].

Due to the effects that PERV recombinants could have in PERV expression, recombination of these sequences was also analyzed in a recent study. When PERV γ 1 was analyzed, recombinant sequences of the PERV-A and PERV-C *env* subtypes were detected [26], and it was shown that this recombination could happen naturally [27]. In addition, the recombination event was detected in the *gag*, *pol* and *env* genes of several PERV γ 1 and γ 2 sequences [26]. Finally, recombinant sequences of the *pro-pol* complex have also been detected in PERV γ 2 [28].

Dogs and Cats

Seven canine ERVs were found in different breeds by RT-qPCR expression [33]. The expression of the *pol* gene of this group was detected in 8 organs (liver, kidney, mesenteric lymph node, lung, spleen, jejunum, brain and stomach), but variability among tissues was not detected [33]. However, none of these ERVs seemed to be able to express a complete provirus [33].

Moreover, in a study in which homologous genes of syncytins were analyzed, the *syncytin-Car1* gene was found in dogs and cats [60]. The syncytins are genes derived from the *env* gene of an ancestral ERV and are conserved in 26 Carnivora species [60]. Its expression, as determined by RT-qPCR, was high in the placenta of dogs and cats, while other *env* genes of these species showed variable expression patterns in other analyzed tissues (uterus, cortex, lung, muscle, testis, liver, spleen, kidney, intestine, heart and skin) [60].

Horses

The expression of 842 predicted ERVs was analyzed by RNA transcriptome sequencing in the kidney, jejunum, liver, spleen and mesenteric lymph nodes of horses [38]. A subset of these predicted ERVs (9.3%) was likely to be expressed, although these sequences did not belong to any particular ERV group [38]. However, none of the analyzed ERVs expressed all of their genes [38].

Sheep

Due to the important role of enJSRVs in sheep development, placental morphogenesis and the blocking of its exogenous counterpart JSRV, the expression analyses of sheep ERVs have been mainly limited to this provirus [40]. enJSRVs are highly expressed in the sheep fetus, which may explain some aspects of the pathogenesis of the disease that is induced by the related exogenous JSRV after birth [41].

Using *in situ* hybridization analyses, the strongest expression of enJSRV was detected in the uterus, but weaker expression was found in the lamina propria of the gut and in the bronchiolar epithelium of the lung [61]. In a previous study

Table 3. **Expression analyses of ERVs.**

Species	Experimental Methods	*In Silico* Methods	Tissues with Retroviral Expression		
			High	**Low**	**Similar**
Sus scrofa	RT-PCR, Western blot, immuno-histochemistry [a], qPCR [b]	NA	Lungs, spleen and lymph nodes, epithelial kidney cell line	Cerebrum, myocard, muscle, colon and kidney	
Canis familiaris	(RT)-qPCR [c]	NA	Placenta		Liver, kidney, mesenteric lymph node, lung, spleen, jejunum, brain and stomach
Felis catus	RT-qPCR [d]	NA	Placenta		
Equus caballus	RNA transcriptome sequencing [e]	NA			Kidney, jejunum, liver, spleen and mesenteric lymph node
Ovis aries	RT-PCR [f]	NA		Peripheral blood mononuclear cells	Heart, kidney, liver, lung, spleen and fetal thymus
Bos taurus	RT-PCR [g]	NA	Placenta		
Gallus gallus	RT-PCRh, mRNA-seq [i]	EST database [j]	Embryo fibroblast, gonads		

NA, not analyzed.

[a] [58]; [b] [30]; [c] [33, 60]; [d] [60]; [e] [38]; [f] [45]; [g] [66]; [h] [54]; [i] [57]; [j] [54].

based on sensitive reverse transcription-PCR assays, low levels of enJSRV expression were detected in several sheep tissues of different origins [62]. It seems that transcription of enJSRVs in the endometrial epithelia of the ovine uterus is related to conceptus-endometrium interactions during the peri-implantation period and early placental morphogenesis [63].

Interestingly, it has been demonstrated that putative protective enJSRV variants are expressed in alveolar type II cells (AECII), which are the major target of exJSRV [64], and that the signal peptide of the envelope of this variant plays a major role in blocking exJSRV entry [65]. In addition to enJSRVs, the expression of OERV γ 1 and γ 2 has also been analyzed by RT-qPCR, and these ERVs have been detected in 6 tissues (heart, kidney, liver, lung, spleen and fetal thymus) but not in peripheral blood mononuclear cells [45].

Cattle

Because BERVs are involved in the morphogenesis of the placenta [66], this topic has also been widely studied in cattle. By RT-qPCR, the expression of two BERVs of Class II, termed BERV-K1 and BERV-K2, was detected in the placenta and bovine trophoblast cells [66]. In addition, expression of the putative gene bERVE-A, which is an ERV-derived gene, was detected in binucleated cells, which is a specific trophoblastic cell type [67]. More specifically, expression of bERVE-A and the *env* gene of BERV-K1 was detected in trophoblastic tissue during the peri-implantation period, and their expression was enhanced in trophoblastic cell differentiation and binucleation [68]. In another approach using the transcriptomes of different stages of bovine

conceptuses, the expression of 284 *env*-derived loci was also detected [50]. Thus, it could be likely that ERVs or ERV-derived genes are important for placentation, as in other mammals such as humans, mice and sheep [4].

Chickens

The expression of different ERVs has been analyzed in chickens by RT-qPCR and *in silico* analyses based on the EST database. For example, in chicken embryo fibroblasts, the expression of ChiRV1 ERV was detected [54]. Another ERV, termed OVEX1, was expressed asymmetrically in chicken gonads depending on the sex and the development stage of the gonad. Therefore, we can infer that OVEX1 is important in the physiology of the chicken ovary [55]. Accordingly, the expression of many ERVs that were detected by Retrotector[©] was tested by mRNA-seq in embryo fibroblasts, and many were shown to be partially translated, especially their *gag* gene [57].

The expression results in the seven species are summarized in (Table **3**).

DOMESTICATION OF ERVs IN DOMESTIC ANIMALS

As mentioned above, ERVs play an important role in the morphogenesis of the placenta of cattle and sheep, as in other mammals [4]. Indeed, the recruitment of ERVs and their reuse as a functional part of the host genome, which is also known as co-option or domestication, has facilitated the evolution of the placenta [69]. Among ruminants, the *Syncytin-Rum1* gene has been detected in 16 species, and it originated as an *env* gene of an ERV [70]. In addition, it has

been proposed that the gene *Fematrin-1*, which is a domesticated *env* gene of BERV-K1 ERV, could explain the morphological diversity of placentation in ruminants [71]. In dogs and cats, a gene termed *Syncytins-Car1* has been detected, and this gene belongs to a degenerate ERV [60]. In addition, these genes have been detected in 26 species of the Carnivora order [60]. Thus, those related to the morphogenesis of the placenta are a good example of the impact of ERVs in the genomes of domestic animals.

Due to the variety of placental morphogenesis and the independent co-option for this task, it is difficult to summarize a general model for the role of ERVs in placentation. However, it has been proposed that ERVs facilitate the evolution of placenta and, specially, their involvement in trophoblasts [72].

CONCLUSION AND FUTURE DIRECTIONS

Without a doubt, our knowledge of endogenous retroviruses in domestic animals has improved notably over the last years. The growing interest in these genetic elements and their role in non-model organisms, the availability of the genomic data of domestic animals, the application of experimental procedures in non-model organisms and the development of new computational tools have contributed to this improvement. In addition, the new genomic data available about ERVs in domestic animals could be helpful to confirm or discover new findings on the evolutionary implications of ERVs showed in model animals and primates. Finally the ERVs could be used to study the domestication itself and to infer the evolutionary history of infections in domestic species; domestication processes could have affected infection dynamics and, as a result, the probability of ERVs becoming incorporated into a specific genome.

However, there are still aspects regarding ERVs in domestic animals that are unclear. The release of new genomes will be helpful to study the presence of ERVs in other domestic animals in greater depth and to establish the evolutionary history of different ERV groups or families and their distribution among breeds (as has been done in sheep). It will also be important to study the expression of ERVs and the consequences that their expression has for the host: some are beneficial, for example, in the placenta, and others are detrimental, causing infectious viruses. It is also worthy to study the adaptation of the host to their ERVs and the mechanisms that evolve to keep ERVs under control (e.g., in sheep). In conclusion, the most challenging task will be the compilation and systematization of all information available regarding ERVs and the creation of a general framework to explain the dynamics and implications of ERVs.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

ABBREVIATIONS

ERV = Endogenous retrovirus

LTR = Long terminal repeat

PERV = Porcine endogenous retrovirus

MYA = Million years ago

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