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HOW RETROTRANSPOSONS SHAPE GENOME REGULATION

Paolo Mita and **Jef D. Boeke**

Institute for Systems Genetics, Department of Biochemistry & Molecular Pharmacology, NYU Langone Medical Center, 430 E 29 St., New York NY 10016 USA

Abstract

Retrotransposons are mutagenic units able to move within the genome. Despite many defenses deployed by the host to suppress potentially harmful activities of retrotransposons, these genetic units have found ways to meld with normal cellular functions through processes of exaptation and domestication. The same host mechanisms targeting transposon mobility allow for expansion and rewiring of gene regulatory networks on an evolutionary time scale. Recent works demonstrating retrotransposon activity during development, cell differentiation and neurogenesis shed new light on unexpected activities of transposable elements. Moreover, new technological advances illuminated subtler nuances of the complex relationship between retrotransposons and the host genome, clarifying the role of retroelements in evolution, development and impact on human disease.

INTRODUCTION

Transposable elements (TE) are genomic units able to move within the genome of virtually all organisms [1]. More than half of our genome and likely over two-thirds of it [2] consists of TEs or their ancient relatives. Notably, in some plants such as maize, gene coding regions are just small islands “floating in a sea of retrotransposons” [3]. Transposons were discovered in maize and described as “controlling elements” by Barbara McClintock in the late 1940s [4]. TEs were considered “genomic junk” [5] until more recent works highlighted the substantial impact of mobile elements on shaping the genome and potentially rewiring its control [6–8]. Previous reviews give comprehensive historical analysis of the different perspectives, considering transposable elements either “controlling elements” with major functions in genome regulation, “selfish DNA” owing only to their selfish purpose of expansion [9] or, more recently “both mutualistic and extreme parasites” [6].

TEs are usually subdivided into two major classes: retrotransposons (class I) that use a “copy and paste” process for their replication and expansion and DNA transposons (class II) that use a “cut and paste” mechanism. Of these, only retrotransposons are active in the modern human genome and represent a prominent force of genomic evolution [6,10], although other mammals, notably certain bat taxa, have much more diverse TE populations,

including active DNA transposons [11,12]. Retrotransposons' classification and molecular features are summarized in Figure 1; see previous reviews [6,13-15]. Retrotransposons are classified into two categories: LTR (Long Terminal Repeat)-retrotransposons [16], and non-LTR retrotransposons including LINEs (Long Interspersed Nucleotide Elements), SINEs (Short Interspersed Nucleotide Elements) and in humans, SVAs (SINE-VNTR-*Alu* elements). LINEs, SVAs and LTR-elements are transcribed by RNA polymerase II while SINEs are transcribed by RNA polymerase III. Retroelement RNA is post-transcriptionally retrotranscribed and the cDNA is integrated into a new genomic location, a process called retrotransposition. The LINE elements are the only autonomous retrotransposons; SINEs and SVA elements depend on LINE-1 machinery for retrotransposition. Retrotransposons have distinct evolutionary histories. LTR endogenous retroviruses are clearly evolved from ancient viral infections of the germ-line and are maintained vertically in the germ line. Endogenous retroviruses encode Pro, Gag, Pol and sometime Env-like proteins like their exogenous cousins. Non-LTR retrotransposons like L1 are thought to have a common ancestor with group II introns, which often encode a reverse-transcriptase and can self-splice; they are likely ancestral to the modern spliceosome [17]. The *Alu* SINEs derive from cellular 7SL RNA, the RNA subunit of the signal recognition particle [18]. SVA elements are composite "patchworks" originating from distinct retroelements. Retroelements' distinct origins underlie substantial differences in life-cycles, functional behavior and host-interactions; these differences have to be taken into account when retrotransposons are considered collectively.

The repetitive nature of TEs makes them challenging to map onto a reference genome especially in the age of short read DNA sequencing. Therefore, despite their abundance in animals and plant genomes, the study of TEs, their evolution and behaviour and ultimately their impact on the host has lagged behind. Recently, technological advances in bioinformatics [19] including creation of comprehensive databases of annotated repetitive elements such as RepBase [20] and Dfam [21], incredible advances in DNA sequencing including long-read methods [22,23] and clearer knowledge of the genome from an ever-expanding variety of organisms (i.e. [24]), have injected new technological power into "transposonology".

In recent years, the discovery of retrotransposon activity in somatic cells of the brain or their expression in specific stages of development and cell differentiation [23,25-28] raised the possibility of an actual beneficial role conferred by retrotransposon activity on the host, for example in neuronal plasticity [24,27,29]. Additionally, the study of somatic insertions in cancer [30-32] and the strive to elucidate the role of active retrotransposons in human pathologies [33,34], underscore the importance of retrotransposons not only on an evolutionary time scale but also in more dynamic and sometimes deleterious processes. These include epigenetic control and transcriptional regulation, cell differentiation and reprogramming [28], cancer initiation and progression [14], as well as processes like normal aging [35-37].

Here we briefly cover the consolidated impact of retrotransposons on genome architecture and genome evolution with particular focus on human retrotransposons and new findings validating a more dynamic impact on retrotransposon-induced regulation such as epigenetic

and gene transcriptional regulation. These more recently identified effects of transposon mobilization may be less “disruptive” and imply a more subtle reshaping of genome control as opposed to gross effects on its structural organization. The more recent data supporting “positive” effects of retrotransposon activation will be discussed in light of the rediscovered view of retrotransposons as major drivers of genome evolution, a concept postulated by McClintock and by Britten and Davidson [38,39] more than a half-century ago.

RETROTRANSPOSON-INDUCED STRUCTURAL GENOMIC REORGANIZATION AND GENETIC INSTABILITY

Retrotransposon-induced genetic rearrangements

Because of their repetitive nature, retrotransposons are a source of chromatin instability and genomic rearrangements with deleterious consequences [15,40]. In the human genome, insertional inactivation and other genome rearrangements lead to a wide spectrum of genetic diseases including hemophilia, thalassemia and muscular dystrophy [41]. Retroelement-induced genetic rearrangements can be passive (due to the repetitive nature of TE) or active (directly caused by retrotransposition events) and of several types (reviewed in [13,15,40,42]): (I) non-allelic homologous recombination [41] mainly driven by *Alu* elements in humans, (II) insertional mutagenesis due to the “hopping” of retrotransposons within gene coding sequences; it causes diverse effects on target gene expression depending on intragenic location, orientation, length of the inserted sequence and other factors, (III) 3’ and 5’ transduction during which flanking genomic regions can be co-retrotransposed with the retroelements [43], (IV) trans-mediated mobilization of RNAs by “template switch” as is common with U6 RNA or by “template choice” as for the creation of processed pseudogenes (for more details see [44]).

Retrotransposon-induced changes in genome topology

Numerous lines of evidence demonstrated the organization of chromatin into nuclear domains [45] able to affect genome regulation and gene expression [46]. Heterochromatization of repeats through the processes described below have an effect on the topological distribution of genomic regions [46-49] and on the 3D organization of chromatin, likely through CTCF/cohesin binding to TEs [50,51]. It has been shown that at least 40% of the CTCF binding sites in the mouse genome (22.8% in human) are derived from SINEs elements [51]. The actual percentages are likely to be substantially higher thanks to ancient transposition events that can no longer be recognized due to mutational erosion. However, direct evidence for such retroelement-dependent reorganization is still lacking. Chromatin conformational studies using e.g. Hi-C focused on retrotransposons and their relevance in the evolution of genomic looping and long-range interactions could add a new dimension to the established relevance of TEs to the diaspora of TSS and TF binding sites discussed below [8,51]. It would be interesting to compare the topological distribution of common and species-specific retrotransposons in nuclei of cells from closely and distantly related organisms to evaluate the relevance of retroelements to extant genome architecture.

RETROTRANSPOSON-INDUCED CHANGES IN GENOME REGULATION

Transposon-induced changes in gene expression

Most genome scale work on retrotransposons examines TEs and flanking sequences in genomes of model organisms. This approach overlooks those insertions selected against during evolution that likely had the strongest effect on neighboring sequences. The majority of retrotransposon insertions are unsurprisingly found in non-coding or intronic regions. The effect of these insertions is usually thought to be neutral or affecting processes like alternative splicing, premature termination, long-range interactions or the creation of new regulatory regions. Han et al. [42,52] proposed a model according to which antisense LINE-1 insertion in an intron decreases RNA polymerase II processivity, reducing transcription rate of the genes in which L1 is inserted. This model called the “rheostat hypothesis” was demonstrated *in vitro* but direct evidence for it is limited. More recently, methylation status of intronic TEs in *Arabidopsis thaliana* was correlated with lower transcription of genes with TE insertions [53].

A classical example of retrotransposon dependent gene regulation in mice is the *agouti* gene (*A*). The efficiency in silencing an IAP (Intracisternal A-type Particle) element upstream of this gene correlates with a range of coat colors from yellow when the IAP is completely silenced to dark brown when the IAP is active [54].

A rigorous comparison of whole genome RNA expression with DNA sequencing identifying novel sites of insertion of in vitro expressed and “trackable” retroelements (i.e. recoded retroelements easily distinguishable from endogenous sequences [55]) will help answer these questions. Also, more systematic knowledge about the influence of stress or environmental cues on epigenetic control of retrotransposons as well as impact of transposons on phenotypic plasticity is still lacking. The stochastic and sometime incomplete nature of epigenetic silencing of retrotransposons may help explain and model complex systems such as cancer progression, lineage differentiation and brain complexity.

Epigenetic control and retrotransposon repression

Repetitive element mobilization represents a “dangerous” process for the host cell/organism when viewed from an individual perspective. Indeed, a clear “arms race” exists between retrotransposons and host defense mechanisms [56,57]. Conversely, it has been suggested that epigenetic control of the genome (a process likely rooted in transposon control, see below) paradoxically favored retroelement expansion by inhibiting excessive homologous recombination [58]. However, several mechanisms such as DNA and histone methylation and RNAi, actively suppress retrotransposon expression. The epigenetic mechanisms controlling retroelements may well follow retrotransposons during their movement “around” the genome and thereby modify the epigenetic control of retrotransposition targeted loci [59,60]. Below we describe ways of retrotransposon repression that contributed to sculpt the modern genome and its regulatory mechanisms.

Repression by cellular environment

An important factor that played an essential role in promoting retrotransposon expansion was probably the more permissive transcript survival environment of the eukaryotic cytoplasm, promoted by the 5' cap/3' polyA structure. On the other hand, cytoplasmic retrotransposons with longer mRNA half-life had to deal with the inhibitory effect of the nuclear membrane, which may represent a primitive defense against retrotransposition [61]. It has been proposed that disruption of the nuclear membrane during mitosis may be necessary for the entrance of the retrotransposon RNP particles into the nucleus [62]. The mechanisms that mediate nuclear translocation of retrotransposons are still unknown despite the obvious relevance to retrotransposon life-cycle/activity.

Repression by DNA methylation

DNA methylation is essential to control transposon repression in the germline and undifferentiated cells [63,64]. Recent studies suggest that LTR hypomethylation and activation of HERV-K and HERV-H endogenous retroviruses during early developmental stages directly contributes to pluripotency maintenance [25,26]. In the case of HERV-H, it can provide binding sites for TFs that mediate expression of pluripotency transcripts. Tellingly, HERV-H transcripts were also shown to function as lncRNAs important to maintain pluripotency [65] and HERV-K was shown to protect potentially vulnerable early embryonic cells from exogenous virus infection, suggesting exaptation.

Interestingly, CpG islands created by de novo somatic retrotransposition were shown to be hypomethylated, implying an inability of differentiated cells to silence newly mobilized elements [59]. Moreover, hypomethylated CpG islands create graded influence of hypomethylation on nearby CpGs, a phenomenon termed "sloping shores". Because newly inserted retrotransposons created sloping shores, previously shown to influence neighbouring gene expression, it is likely that retrotransposition events in somatic cells influence gene expression of flanking regions by modifying their methylation status.

Repression by histone modifications

Histone modifications are also essential for retroelement repression particularly in undifferentiated cells [66,67]. G9a [68], Eset/Setdb1 [69,70], KAP1/ZNF proteins [37,71] and Lsd1/ KDM1A [72] repress retrotransposons in embryonic stem (ES) cells. Jenuwein and colleagues [73] showed that in mouse ES cells, Suv39h histone methyltransferase is recruited specifically to intact, full length LINE-1. Recent studies support the idea that retrotransposon and heterochromatin repression is initiated by random recruitment of TFs such as Pax3/9, ZNF proteins and homeodomain TFs [74]. Low-level mRNA transcribed upon random recruitment of these TFs may mediate silencing of repetitive element regions in undifferentiated cells [73,75]. Moreover, long non-coding RNAs (lncRNAs) can mediate HP1 and H3K9me3 independent recruitment of the H4K20me3 methyl transferase enzyme Suv4-20h2 onto non-pericentric or telomeric IAP retroelements in quiescent and terminally differentiated cells [76].

Histone deacetylation is also important for LINE-1 retrotransposition suppression in human embryonic carcinoma cells [77].

These studies collectively demonstrate that retrotransposons are targeted by several epigenetic modifications fundamental for establishment and maintenance of heterochromatin and that could have enabled rewiring of transcriptome regulation through retroelement mobility [54]. A better understanding of the key players in retrotransposon repression will certainly shed light on basic unanswered questions about the molecular mechanisms necessary for the establishment and maintenance of heterochromatin repression.

Repression by RNA interference (RNAi) and piRNAs

RNA interference is another layer of control that host organisms use to down-regulate retrotransposons [78-80]. Of the known RNA interference pathways (siRNA, miRNA, piRNA, rasiRNA, endo-siRNA) retrotransposons seem to involve a complex combination of DICER-dependent and -independent RNAi responses [80,81]. It has also been proposed that the miRNAs evolved from TEs [82]. Interestingly, piRNA-mediated silencing of TEs can spread to adjacent genes, affecting their expression in *D. melanogaster* [60]. Intriguingly, in *Drosophila* germline stem cells (GSC) establishment of heterochromatin by SETDB1 was shown to be essential for expression of piRNA targeting transposable elements [70] supporting a intertwining of transposon expression and host cell chromatin regulation.

Overall, the existence of diverse RNAi mechanisms targeting retrotransposons implies that RNAi control is another genomic process “expanded” way beyond retrotransposon control and that has been exapted and rewired by the host cells in response to TE activity.

RETROTRANSPOSON-INDUCED GENETIC INNOVATION

Retrotransposons can also impact gene regulation simply by inserting their own intrinsic regulatory sequences (promoters, cryptic splice sites, terminators, enhancers and insulators) in new genomic loci upon retrotransposition (Fig. 1)[6]. These regulatory elements can disrupt expression and structure of genes located near or within retrotransposition sites.

Alternative splicing broadens the diversity of protein repertoire produced from a “fixed” genome. Retrotransposition into an intron can alter its splicing through exon skipping, alternative donor or acceptor splice sites, intron retention [10,83] and exonization [84]. The LINE1 retrotransposon (L1) was shown to contain numerous functional splice acceptor and donor sites. L1 mRNA processing through splicing that renders the spliced retrotransposon inactive was proposed to serve as a host defense mechanism against excessively burdensome L1 transcription [85]. Unpublished data from our laboratory also support this hypothesis.

Retrotransposon promoter/enhancer sequences have donated regulatory elements pervasively to many genes and many if not all such sequences are targeted by several host signals and proteins. Despite many predicted transcription factor (TF) binding sites can be mapped on the L1 5’UTR, and on endogenous retroviral LTRs [86], few proteins have been directly shown to regulate retroelement transcription. RUNX3 [87], MeCP2 [88], p53 [89], SRY [90], Sp1 and Sp3 [91], YY1 [92,93] and more recently Oct4, Sox2, Nanog and KLF4 [25,26,94] are proteins demonstrated to mediate retrotransposon transcription. Recent work demonstrated recruitment of SIRT6 protein to the 5’UTR promoter of L1 and its repression through ribosylation of KAP1. Interestingly, SIRT6 recruitment and repression function

decreases with aging, perhaps by redistribution of SIRT6 proteins on DNA damage sites in aged animals or senescent cells [37]. Future efforts should focus on elucidating TFs responsible for retrotransposon transcription in a more comprehensive manner.

Several studies show that retrotransposon regulatory units were expanded by being scattered genomewide through retrotransposition events and were subsequently “rewired” evolutionarily to provide many tissue specific gene regulatory elements (promoters/enhancers) [95]. Regulatory features (i.e. promoter or enhancer regions) of many retroelements have been shown to be co-opted by the host cells (exaptation)[96]. C-GATE is a publicly available catalogue of known putative and directly characterized transposons exapted by their host organisms [97]. These observations led to the hypothesis of relevant evolutionary importance for retroelement activity, e.g. in evolution of humans from the least common ancestor with other great apes [98].

Also, some LTR-retrotransposon derived proteins have been directly incorporated into host cellular processes in a phenomenon defined as “transposon domestication” [99,100]. The phenomenon of domestication/exaptation provides a framework for understanding the fundamental roles played by TEs in shaping genomic evolution in several organisms. These phenomena support the idea of a strong evolutionary benefit in retrotransposon mobilization although this must always be balanced with the clear negative effect at the level of the individual [7-9,51]. According to this viewpoint transposons are “dormant genetic units” with mutagenic and regulatory potential ready to be set into action and mobilized for adaptation to environmental stresses [101] (Figure 2). The concept of “genomic shock” initially hypothesized by Barbara McClintock finally found substantial supporting evidence in more recent studies showing that perhaps the majority of DNA regulatory regions (promoters, enhancers, TF binding sites) evolved from mobilization of TEs. Through various approaches, it has been shown that at least 20% of evolutionary conserved regulatory regions (TSS, enhancers or some TF binding sites) are derived from TEs [8,51,102]. These very comprehensive studies clearly demonstrate evolutionary relevance of retrotransposon mobility to the rewiring and selection of the most “fit” gene networks.

Despite the well-substantiated nature of transposons as “controlling elements”, the stress-induced activation of TEs is still not mechanistically well-characterized [103,104]. Stress activation (i.e. ionizing radiation, DNA damage, nitrogen starvation, severe adenine starvation or heat shock, adenovirus infection and cycloheximide treatment) has been shown for Ty1 in yeast and/or for SINEs and LINE-1 in human cells, but the TFs regulating such activation are mostly unknown. Recent studies demonstrated activation of retroelement activity upon circadian and aging stress [35,105,106]. A genome-wide catalog of factors and signals affecting transcription of L1 and other retrotransposons would be very valuable.

Moreover, domestication and exaptation can also help understanding the more recently described “advantageous” cellular effects of retroelements mobilization. For example, active retrotransposition upon environmental cues such as exercise has been demonstrated in hippocampus [27], an area with high adult neurogenic potential. This observation suggests a potential role of retrotransposition in the expansion of neuronal diversity in response to external stimuli. Controversy over the extent of retrotransposition activity in brain

challenges such a mechanistic role [29,107-110]. In line with such ideas, recent work also demonstrated a fundamental role of L1 expression in fetal oocyte attrition, the process of prenatal elimination of most oocytes [111]. As mention above, HERV-K and HERV-H reactivation have been shown to play a role in maintaining pluripotency in ES cells [25,26,65]. Interestingly, certain retroelements are also reactivated in iPS cells demonstrating that the process of reprogramming and resetting of pluripotency induces and perhaps requires TE expression [112,113].

These studies suggest that exaptation of retrotransposons regulatory elements during cell development and differentiation induces inevitable reactivation of the corresponding retroelements still active in the genome during those same developmental states (as for HERV-H exaptation [26]). Domestication of retroelements proteins (as for HERV-K Env protein [25]), on the other hand, created a more direct need for expression of retroelements during specific cell stages. Finally, somatic reactivation of retroelements in tissues like the brain or oocyte during attrition may represent a type of domestication in the broader sense of the term, as reactivation and mobilization of specific retroelements may facilitate general processes like programmed cell death and neuronal plasticity.

IMPLICATIONS AND PERSPECTIVES

The newly gained information about retroelements made possible by great technological advances in bioinformatics and deep sequencing leaves us with many new questions. How does genome plasticity conferred by retrotransposons respond to different type of environmental stresses and what are the molecular mechanisms driving this stress-induced response? What is the impact of retroelement mobility in processes like cancer, cellular reprogramming and aging? What is the molecular relevance of retrotransposon activity in tissues like the brain or developing germ cells in which retrotransposons are not completely repressed? The more recent perspectives on the subject seem to suggest that in these contexts, TE activity can no longer be considered simply due to spurious and uncontrolled loss of regulation because of the newly identified “beneficial” roles conferred by retrotransposons that suggest the existence of retroelement functions co-opted and “safely” modulated by the host cell. Arguably, these views leave open the idea of “symbiotic retrotransposons” however antithetical this may seem to a dyed in the wool “selfish gene” devotee [9]. Thus, what may seem like TE activation during vulnerable windows in the organism development may in fact have provided an opportunity for exaptation of TEs for very specific cellular functions. It is even possible that controlled retrotransposition might provide a selective advantage in a very defined context (i.e. neuronal plasticity or pluripotency maintenance). Targeted genome engineering methods based on the CRISPR/Cas9 nuclease, may help answer these questions, providing clean *in-vivo* systems for studies of retrotransposon impact. It is now plausible to imagine construction of cells or organisms completely lacking active retrotransposons [114] and therefore determine their role in processes like cell differentiation, neurogenesis, aging, tumorigenic proliferation or genome stability.

The relevance of retrotransposons and TEs to nuclear architecture and 3D genome structure is still underdeveloped. Heterochromatin compartmentalization in distinct nuclear territories

and the increasingly recognized importance of nuclear chromatin topology in processes like gene repression and activation hint at a potentially important role in genome architecture for retrotransposons, one of the major components of heterochromatin. Is retrotransposon mobility able to induce topological restructuring of the genome? Could alteration of retrotransposon repression do so? Are there phenotypic/functional consequences of retrotransposon activity that can be explained by an alteration of nuclear architecture? These questions are still open and surely poised to be answered soon.

Overall, the recent and more “dynamic” and nuanced view of transposons, demonstrates the enormous relevance of repetitive elements to genome control. From an evolutionary standpoint it is fair to consider the modern genome of several, if not all organisms, as a simple “snapshot” of their complex and ever-changing mobilome. The newly proposed “positive” cellular effects of retrotransposons can be explained considering that these effects evolved randomly from the activity of retroelements and have been fixed genomically because of the positive consequences they fortuitously offered to the host organism. The emergence of these apparent retrotransposon-dependent evolutionary “advantages” may help explain “windows” of reactivation that are not only tolerated by the host but actually create opportunities for evolution and adaptation of new functions. In this view the role of retrotransposon activity in human diseases can be considered a failed attempt towards evolutionary advance/adaptation (in the case of genetic disorders) or a “misuse” of the evolutionarily powerful but dangerous weapon represented by TEs (in the case of reactivation of retroelements in cancer).

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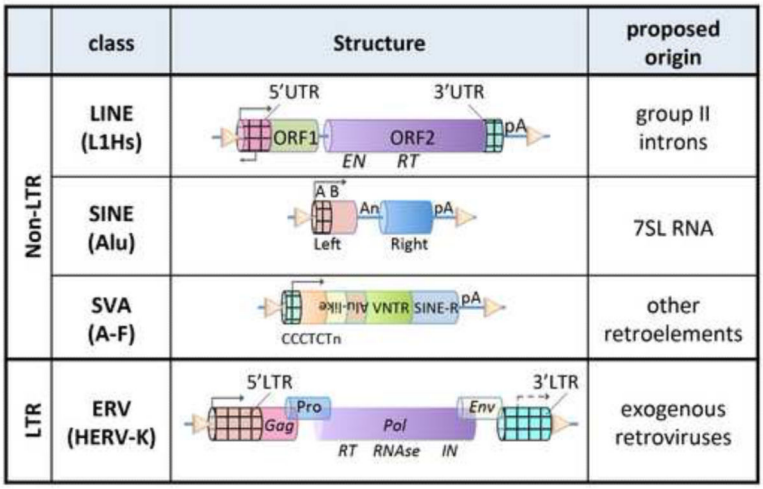

Figure 1. Schematic of human retrotransposons

Retrotransposons (class I transposons) are subclassified into two categories: LTR (Long Terminal Repeats)-retrotransposons, similar to exogenous retroviruses and further divided into multiple sub-families [16], and non-LTR retrotransposons which include LINEs (i.e. L1Hs), SINEs (i.e. Alus) and in humans, SVAs (SINE-VNTR-*Alu* elements, themselves subdivided into classes A-F). Retroelements are thought to have evolved differently and their proposed origin is reported. The transcriptionally active domains of the different retroelements are also indicated with checkered cylinders (see text). The triangles indicate target site duplications (TSD). The inverted "*Alu*-like" tag in the figure indicates the inverted orientation of these domains in SVA elements. Abbreviations: UTR= untranslated regions; ORF=open reading frame; EN=endonuclease domain; RT=reverse transcriptase domain; An= A-rich domain; pA=poly A; A B= domains essential for SINE transcription; VNTR= variable number target repeats; Pro= protease; Gag= group-specific antigen (coat protein) gene; Pol=polymerase (reverse transcriptase); Env=envelope gene; IN=integrase.

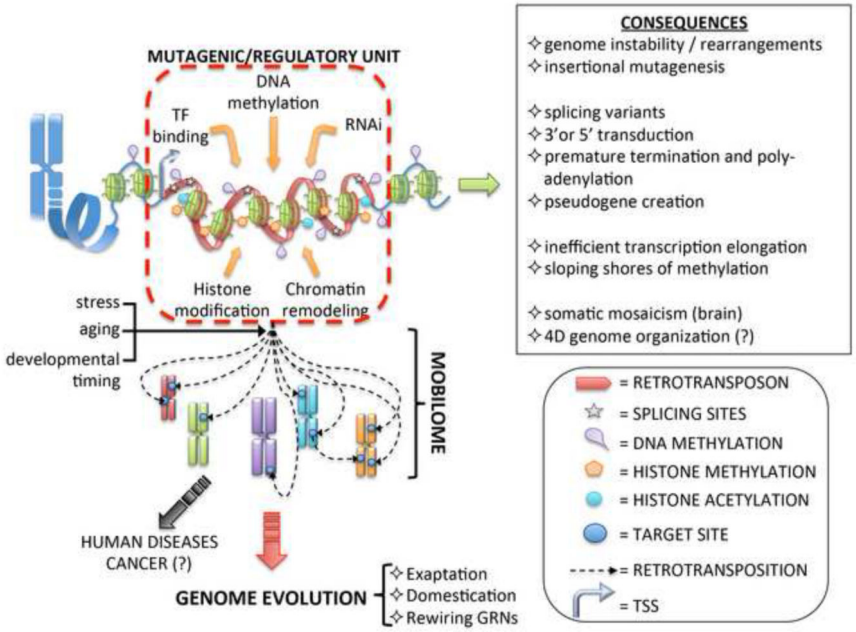

Figure 2. Retrotransposons shape genome regulation

Retrotransposons contain several DNA controlling elements (transcription/enhancer domain, splicing signals, transcription factor (TF) binding sites, repression signals etc.) mobilized as part of retrotransposon activity in "jumping around" the genome. The immediate effect of retrotransposon activity is usually deleterious for the host cells (see top right insert and [10،13]) and in humans may lead to diseases such as cancer (black arrow). From an evolutionary standpoint retrotransposons can be defined as mutagenic units able to rewire and expand gene regulatory networks (GRNs) (red arrow). Stimuli such as stress, aging and specific developmental cues induce retrotransposon mobilization. Upon jumping, retrotransposon functional units can be exapted by the cell and in some cases retrotransposon features can be "domesticated" and incorporated into host cell functions, such as stem and germ cell regulation.