

On the Concept Of Retrotransposons: Controlling Genome and Making Stress Memories

Dimitrios Noutsopoulos

Dimitrios Noutsopoulos, Laboratory of General Biology, Department of Health Sciences, Medical School, University of Ioannina, 45 110 Ioannina, Greece

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Correspondence to: Dimitrios Noutsopoulos, Laboratory of General Biology, Department of Health Sciences, Medical School, University of Ioannina, 45 110 Ioannina, Greece.

Email: dnoutso@cc.uoi.gr

Telephone: +30-26510-07573

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ABSTRACT

Retrotransposons constitute discrete genetic entities that have attained a large fraction of mammalian genomes during evolution. Their inhabitation as well as their functional impact on host genome has definitively revised the initial viewpoint of "junk DNA". Nowadays, it is widely accepted that retrotransposons may control genome through a variety of mechanisms, affecting different cellular processes. Here, I survey their impact on genome architecture and function with an emphasis on their interwoven relationship with stress.

Key words: Retrotransposon; Retrotransposition; Stress; Adaptation; Cellular memory

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List of abbreviations

TE, transposable element; LTR, long terminal repeat; LINE, long interspersed nuclear element; SINE, short interspersed nuclear element; ERV, endogenous retrovirus; SVA, SINE-R_VNTR_Alu; VNTR, variable number tandem repeat; siRNA, small interfering RNA; miRNA, microRNA; piRNA, Piwi-interacting RNA; rasiRNA, repeat-associated small interfering RNA; endo-siRNA, endogenous small interfering RNA; S/MAR, scaffold/matrix attachment region; SNV, single nucleotide variation; CNV, copy number variation; lncRNA, long noncoding RNA; UTR, untranslated region.

INTRODUCTION

Mammalian genome fluidity is the consequence of "molecular struggles" taking place in the course of evolution. Abiotic and biotic environmental challenges constituted the driving force of such struggles, with repetitive DNA representing their living traces within genome. Transposable elements (TEs) - a universal genomic feature of all organisms - are mobile repetitive genetic elements that are evolutionary fixed into host genomes^[1]. On the basis of the mechanism, by which they move throughout genome, they are classified into two major classes: class I or retrotransposons and class II or DNA transposons (Figure 1A). The mobilization of DNA transposons occurs through a conservative two-step mechanism, so-called "cut and paste", comprising the excision of the element from one genomic site and its subsequent integration into a new one. DNA transposons, in lack of evidence for present-day transpositional activity, are considered genetic relics within modern mammalian genomes. On the other hand, retrotransposons move via a replicative "copy and paste" mechanism, which requires: (a) the production of a retrotransposon RNA-intermediate molecule, (b) its reverse transcription into cDNA and finally (c) integration into the genome^[1,2]. Retrotransposons are subdivided in two broad groups, long terminal repeat (LTR) and non-LTR retrotransposons, both retrotranspositionally active in mammals (Figure 1B).

Mammalian retrotransposons have distinct evolutionary origins. LTR retrotransposons have originated from serial germline retroviral infections during evolution, and thereafter inherited in a Mendelian fashion^[3]. On the other hand, for non-LTR retrotransposons is proposed to derive from group II introns^[4], cellular RNAs^[5-10] and

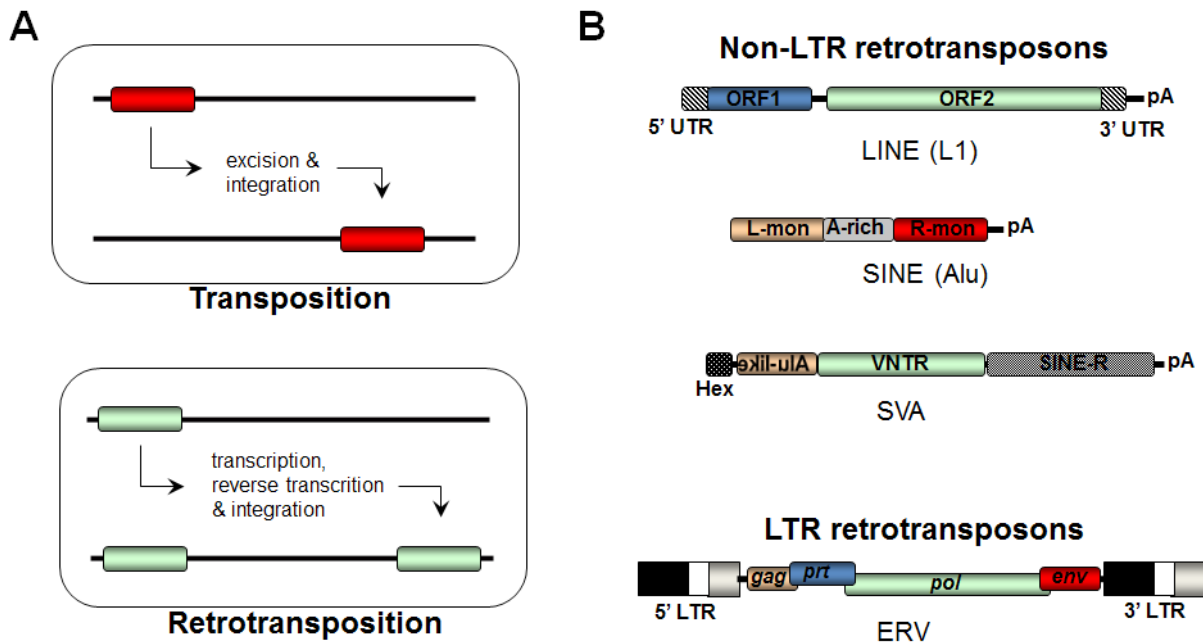


Figure 1 Mobilization mechanisms and types of transposable elements in mammals. (A) Schematic illustration of mobilization mechanisms of mammalian transposable elements. (B) Types of transposable elements in mammals. Abbreviations: LINE, long interspersed nuclear element; SINE, short interspersed nuclear element; ERV, endogenous retrovirus; SVA, SINE-R_VNTR_AlU; UTR, untranslated region; ORF, open reading frame; pA, poly (A); L-mon, left monomer; R-mon, right monomer; Hex, hexamer domain; Alu-like, Alu-like domain; VNTR, variable number tandem repeats; SINE-R, SINE-R domain; LTR, long terminal repeat; gag, group-specific antigen; prt, protease; pol, polymerase; env, envelope.

other distinct retrotransposons^[11]. Even if the strategies recruited to occupy host genome remain an open question, retrotransposons have been co-evolved with the mammalian genome. Nevertheless, the colonization of mammalian genomes by retrotransposons represents a state of stress. Here, it is briefly highlighted the vast repertoire of retrotransposon modes of action and their impact on genome architecture and function. Moreover, considering that their activity can be induced by different factors and particularly stress^[12], I discuss the aspects of retrotransposon-activated responses in terms of adaptability and propose their role in stress-induced cellular memories.

A CHALLENGING TIMELINE: FROM PARASITES TO CONTROLLING ELEMENTS VIA EXAPTATION

In the mid-nineteen forties the groundbreaking work of Barbara McClintock challenged the dogma that eukaryotic genomes are stationary entities by introducing the notion of dynamic genome. The discovery of mobile genetic elements and her foreknowledge to call them "controlling elements"^[13] have introduced a concept far outside of the scientific mainstream. Two decades later, in support of McClintock's view, Britten and Davidson proposed that TEs act as regulators of host genome functions^[14,15]. However, controlling elements' concept has been greeted with skepticism as well as disregard^[16], and as a consequence, terms such as molecular parasites, "selfish DNA" or "junk DNA"^[17,18] have been used for TEs. Though, the concepts of controlling elements and dynamic genome have been widely accepted in the nineteen eighties. To this direction, three milestone events played central role moving the field forward. First, McClintock received a number of prestigious awards, with the Nobel Prize in Physiology or Medicine in 1983 being the apogee for the discovery of TEs. Second, Boeke and colleagues deciphered the mechanism of mobility of a class of TEs in yeast. He called them retrotransposons by virtue of the prerequisite of an RNA-intermediate

and its subsequent reverse transcription prior to its insertion into a new genomic site^[2]. Third, in the late-nineteen eighties Kazazian's seminal work uncovered a hemophilia A-causing LINE-1 insertion, demonstrating present-day mobilization of TEs in human beings^[19].

Since then, a flourish of works has revised the designation of TEs as "selfish" or "junk". Brosius and Gould were the pioneers, introducing the previously postulated term "exaptation"^[20] in the biology of TEs. They proposed that a number of TEs have been exapted, i.e. acquired a new function necessary for the host genome^[21,22]. The Human Genome Project confirmed the "exaptation hypothesis", as it provided evidence that TEs can contribute regulatory elements as well as create new genes in the human genome^[23]. Moreover, the availability of the first human genome DNA sequence draft revealed that about half of the human genome derives from TEs^[23], probably an underestimate but definitely a surprising finding. Indeed, a few years later it was estimated that approximately two-third of the human genome is TE-derived^[24]. Thus, it is undoubtedly too widespread to be the genomic junkyard. The "metamorphosis" of TEs from parasites to controlling elements has primarily supported by the lengthy record of exapted TEs^[25-28], and also from the astonishing genomic load in TEs sequences^[23,24]. The post-genomic era gave rise to large-scale genomic projects. These allowed to gain insight into the functional contribution of TEs to host genome, unraveling their functional impact on host genome^[29-33] (Figure 2). Our knowledge concerning the "dark side" of the genome is still lagging. Despite this, we now know that retrotransposons are active in the modern mammalian genomes, acting in a binary fashion either as structural determining components or functional controlling entities.

RETROTRANSPOSONS: A WEB OF SOPHISTICATED GENOMIC SCULPTORS AND REGULATORS

If, as many believe, the life is originated from an "RNA world" with the genetic material converted subsequently into DNA,

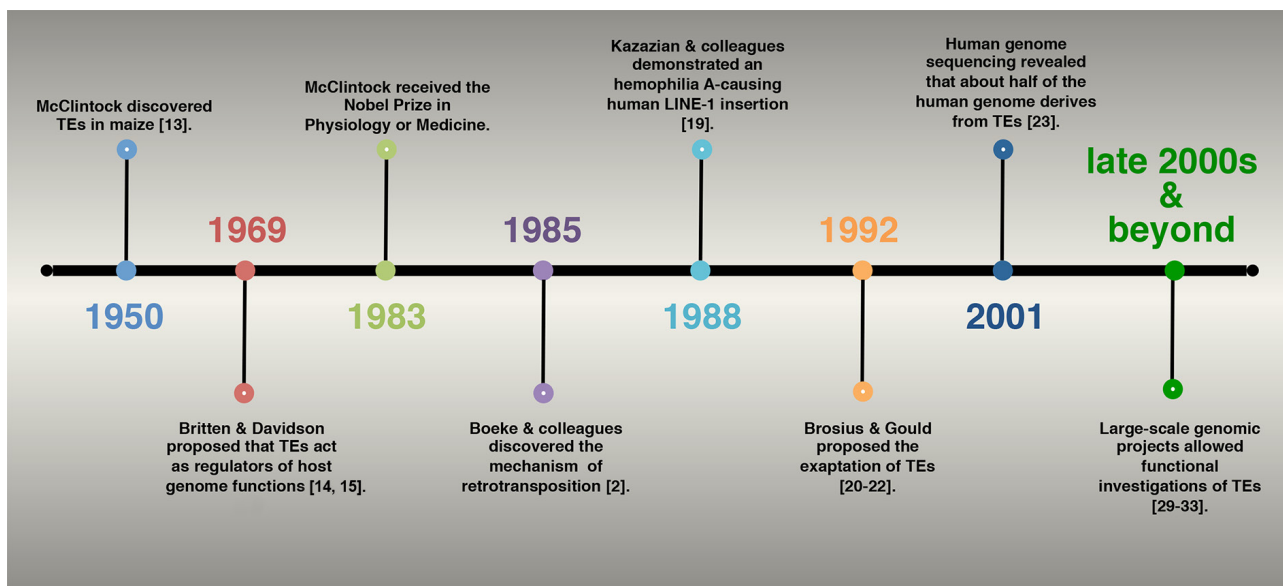


Figure 2 Timeline of milestone discoveries or events on the research field of transposable elements.

retrotransposons may have acted as very early participants in genome formation^[34]. Overcoming the selective pressure exerted during the distant evolutionary past, they are fixed and co-evolved in the ever-changing mammalian genomes. Hence, host genome has taken advantage of retrotransposons to shape its landscape as well as improve its homeostatic and regulatory mechanisms.

Retrotransposons occupy the most part of mammalian genome^[23,24,35-37]. Taking into account the estimation that TEs load may exceed two-thirds of the human genome^[24] as well as their capacity to mobilize leading to genome restructuring, then one can easily deduce that they constitute prevailing regulators of nuclear ecology. To ensure as much as possible the integrity and fidelity of genetic information flow, the cell has evolved several control mechanisms to regulate retrotransposon activity^[38-40]. The epigenetic control of genome, a process likely originated in response to TEs activity, through several mechanisms such as cellular environment, DNA methylation, histone methylation and RNA interference pathways (siRNA, miRNA, piRNA, rasiRNA, endo-siRNA) previously reviewed^[38,41-46], is responsible for retrotransposon repression. Nevertheless, nowadays retrotransposons are active playing major roles in the plasticity and regulation of the host genome.

From a structural point of view, first, retrotransposons represent principal structural genomic components constituting the bulk of chromosome domains such as centromeres, pericentromeres, telomeres and microsatellites^[38,47,48]. Their presence in centromeric and pericentromeric regions denotes their possible contribution on chromosome replication and distribution. Moreover, their preferential insertion in telomeric regions may be involved in telomere integrity^[49], even if such a prevention mechanism of chromosome shortening remains to be elucidated in mammals. Second, retrotransposons may act as building blocks for heterochromatin formation contributing to the organization of chromatin into nuclear domains as a consequence of their accumulation in defined genomic regions as well as their epigenetic silencing^[50,51]. It is known that scaffold/matrix attachment regions (S/MARs) are DNA sequences, which anchor the chromatin loops to the nuclear scaffold/matrix and have important role in chromatin organization^[52]. S/MARs appear

to be affected by retrotransposons given that almost half length (~55%) of human S/MARs is enriched in retrotransposon-derived sequences^[53], while ~14% of the mouse counterpart represents target sites for integration of mouse endogenous retroviruses^[54,55]. Third, they can sculpt genome structure having a profound impact on genome variation via rearrangements, such as single nucleotide variations (SNVs), copy number variations (CNVs) (indels) or larger structural variations. Such retrotransposon-induced rearrangements can be passive, due to their repetitive nature as well as their high sequence homology, or active as a direct result of retrotransposition events^[56-67]. Intriguingly, retrotransposition constitutes an important agent for generation of genetic variation^[64-81] being responsible for 20% of the genome structural variation in humans^[81]. Overall, retrotransposon-induced recombination seems to have a fundamental role in creation of genomic stability, diversity and plasticity. This is further supported by the existence of a high number of Holliday junctions, key intermediate structures in all recombination types (homologous recombination, non-homologous recombination and replicative recombination), inside the sequences of all human retrotransposon families^[82].

As regards retrotransposons' functional contribution, they are evolutionarily inhabited the host genome by providing regulatory sequences or participating in regulatory gene networks, thus having a great impact on several cellular processes. Their main effect on host genome originates from the regulatory role that they exert in gene expression. The possession of *cis*-regulatory elements rendered them the largest genomic pool of active and latent gene regulatory sequences. Moreover, their ability in replicative transposition throughout the genome can result in a genome-wide dispersion of such regulatory elements^[83]. Numerous cases of significant changes in gene expression, mediated by either retrotransposon-associated local chromatin signatures or retrotransposon insertions, have been documented in the literature. Retrotransposons can influence host genes by providing promoters/enhancers, transcription factor-binding sites, splice sites and termination sites^[1,42,80,83-85]. Bioinformatics studies revealed that many gene promoters or alternative promoters are derived from retrotransposons^[28,86]. Faulkner and colleagues showed that retrotransposons constitute an integral part of the

cellular transcriptome and influence the transcription of nearby genes. Noteworthy, they documented that 18% and 31% of total transcription start sites in mouse and human, respectively, are located within retrotransposon sequences^[20]. Beyond protein-coding genes, retrotransposons provide promoters and enhancers for long noncoding RNAs (lncRNAs)^[84,87-89]. In addition, a large number of gene enhancers are "donated" by retrotransposons, providing the ability of tissue- and species-specific gene expression^[84,90,91]. Of interest, a recent bioinformatics survey of del Rosario and colleagues identified 14,546 TE-derived regions as possible candidate anthropoid lineage-specific enhancers^[92]. As yet, we still know little about the host factors, which are important for retrotransposon transcription. *In silico* analysis approaches have recorded a vast number of putative transcription factor-binding sites mapped on retrotransposons^[93,94]. Nevertheless, experimental data demonstrating the direct regulation of retrotransposon expression pointed out only eleven transcription factors (namely p53, Oct4, Sox2, Nanog, RUNX3, MeCP2, SRY, Sp1, Sp3, YY1 and KLF4) binding on their promoters^[42].

Retrotransposons are also determinants of regulation of host gene expression at the post-transcriptional level. First, RNA editing and splicing, processes that may be coordinated in mammals^[95], can be affected by retrotransposons. More than 90% of A-to-I RNA editing sites in humans are found within Alu elements^[96-98]. Considering that approximately 75% of all known human genes bear Alu sequences within their introns and/or untranslated regions (UTRs)^[99], edited intronic Alu elements may have an impact on the transcript metabolism^[98]. Moreover, retrotransposons can influence splicing through exon skipping^[100-105], alternative donor or acceptor splice sites^[106], shift of splicing patterns from constitutive to alternative^[107], induction of intron retention and exonization^[108-111]. Second, an outstanding feature of retrotransposons is translational control. SINE retrotransposons can either enhance or repress mRNA translation^[98]. Notably, SINE and LTR retrotransposons are able to inhibit protein synthesis under stress conditions. It was documented that human Alu retrotransposon RNA acts as a *trans*-acting transcriptional repressor during the cellular heat shock response by binding RNA polymerase II and entering these complexes at promoters *in vitro* and in human cells^[112]. Likewise, mouse VL30 retrotransposon transcripts bound to polyribosomes lead to inhibition of translation and cell death following induced cerebral ischemia^[113]. Third, retrotransposons are capable of altering epigenetically host gene expression^[1,106]. Their regulation, through different epigenetic systems^[38,41-46], has established a close relationship between the expression of a given retrotransposon and the respective of an adjacent gene. Interestingly, host mechanisms are often involved in altered gene expression, as the formation of heterochromatin by retrotransposons-targeting repressors can subsequently spread to adjacent genes^[38,83,91]. The phenomenon of heterochromatin spreading, called "position effect variegation", was initially described in *Drosophila melanogaster*^[114]. Position effect variegation associated with retrotransposons is a potential consequence of their presence, notwithstanding there are few documented examples of heterochromatin spreading into adjacent genes from retrotransposons^[115-118]. Recently, studies have shed light on unforeseen insights into gene expression regulation, documenting RNA-associated mechanisms of retrotransposon-mediated epigenetic regulation of gene expression. A significant number of retrotransposons produce small RNAs, such as siRNAs, miRNAs or piRNAs, which can alter *in trans* gene expression^[91,119]. Furthermore, retrotransposon transcripts act themselves as lncRNAs, affecting gene expression as exemplified for human ERVH and mouse VL30 retrotransposons^[88,120-122].

RETROTRANSPOSONS AS DETERMINANTS OF STRESS-ACTIVATED RESPONSES AND CELLULAR MEMORIES

The corollary of retrotransposons' regulatory effects resides in their contribution to genome evolution, modulating several cellular processes mainly through the increase of genome plasticity, creation of pseudogenes as well as creation and remodeling of gene regulatory networks^[83,123]. A flourish of works has documented the involvement of retrotransposons in embryogenesis, cell differentiation, pluripotency, cell cycle, DNA repair, aging, genomic imprinting, X-chromosome inactivation, behavior, metabolism and immune responses^[42,91,124-137]. However, besides their beneficial impact on host cell, the perturbation and/or loss of cellular control mechanisms may lead to the onset of genetic or multifactorial diseases^[80,138,139].

So far, it is known that retrotransposon activity, concerning their transcription and retrotransposition, is induced during cellular processes among them cell proliferation and differentiation, as well as by numerous stress factors such as heavy metals, oxidative stress, UV irradiation, viral infection, and drugs^[1,12,74,91,128,140-144]. Nevertheless, our knowledge concerning the biology of TEs is still rudimentary. Despite a significant research progress made, the determination of a common denominator between heterogeneous stimuli, capable of activating a portion greater than half of our genome, remains an open question. McClintock envisaged that TEs elicit a highly programmed response intended to minimize the impact of stress^[145]. But, when we refer to stress what we mean. Stress is defined as a state in which homeostasis is actually threatened or perceived to be so^[146]. Considering the cell as a microenvironment, both the aforementioned retrotransposon-activating conditions tend to alter the homeostatic balance and, consequently, could be perceived as stress. Stress-mediated retrotransposon activation may result in their induced mobilization or alteration of host gene expression. Depending on the strength of the stress stimulus, such activation may confer adaptation, if the cell profits the recovery of the homeostatic balance^[12], or lead to a vulnerability of the genome^[130,141]. Hence, retrotransposons act as genetic pieces prone to bridge the gap between stress and cellular response. The idiosyncrasy of retrotransposons enables them to provide and disperse *cis*-regulatory elements, which respond genetically and/or epigenetically in a facsimile manner to a given stress stimulus^[83]. Taking into account that these mobile stress-response mediators constitute the most part of mammalian genome, a single stimulus may drive a protracted response in terms of a large genomic extent. In Systems Biology, the induction of a protracted response to a brief stimulus is defined "cellular memory"^[147]. Nowadays, it is widely accepted that: (a) retrotransposons co-evolved with mammalian genomes by providing regulatory DNA sequences or participating in regulatory gene networks^[83] and (b) stress-related epigenetic plasticity might play a role in programming the genome in adaptive responses to environmental stimuli throughout life, via changes in networks of genes^[148]. By extrapolating the aforementioned notion, it is tempting to propose that retrotransposons constitute the principal genomic determinants of stress-induced cellular memories, conferring individual diversity and adaptability in response to stress (Figure 3).

CONCLUSIONS

For a long period of time, retrotransposons were the genomic "black box". Post-genomic era research progress shed light on some

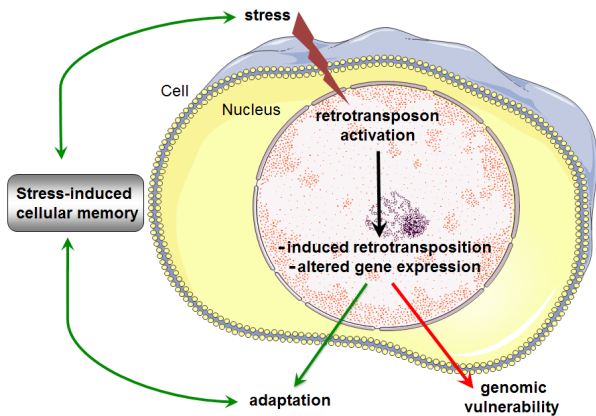


Figure 3 The "retrotransposon-driven stress-induced cellular memory" hypothesis.

aspects of their functional impact on host genome. In her Nobel Prize acceptance lecture, Barbara McClintock stated: "We know nothing, however, about how the cell senses danger and instigates responses to it that often are truly remarkable". We now know that retrotransposons control dynamically mammalian genomes by conferring adaptability in response to homeostasis imbalance or environmental challenges, most likely by making stress-induced cellular memories. Future studies will allow us to unravel mechanistic insights and gain more knowledge on this amazing world that inhabits all of us.

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Peer reviewers: Joanna Gdula-Argasinska