Somatizing the transposons action

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ABSTRACT
The somatic mobilization of transposable elements is more common than previously thought. In this review we discuss how the intensity and the biologic consequences of somatic mobilization are dependent on the transposable elements landscapes of each genome, and on the “momentum” of each particular TE with respect to the mechanisms that control its transposition and the possibility to escape this control. Additionally, the biologic consequences of somatic mobilization vary among organisms that show an early separation between the germline and somatic cells and those organisms that do not exhibit this separation or that reproduce asexually. In the former, somatic transposition can be involved in phenotypic plasticity, detrimental conditions such as disease, or processes such as aging. For the organisms without separation between the germ and soma, somatic mobilization can be a source of genetic variability.

KEYWORDS
genetic mosaicism; somatic mobilization; somatic transposition; transposable elements

Transposable elements: A highly diverse section of the genome

Transposable elements (TE) are DNA sequences that are able to change their position within genomes. They are an ancient part of the genome, probably almost as old as the origin of life. This antiquity has allowed them to evolve a high diversity of sequences, methods of replication and transposition, the enzymes involved in these processes, and mechanisms for their control and activation. Although a unified system for the classification of TEs does not exist, hierarchical structures such as class, order, superfamily and family have been widely used. This wide diversity can be seen in Repbase, which is a database of repeat sequences in eukaryotic genomes. This databank is continuously growing and in December of 2016 has about 40,000 TE sequences, belonging to 65 superfamilies, from 820 different species.

The contribution of TEs to the composition of genomes of different organisms is also diverse. Very few genomes are known to be devoid of TEs. In eukaryotes, the proportion of the genome that is made up of TEs can vary from 3% to 80%. In some species, few TE families are represented, while in others, many families are present. Also, TEs can be autonomous, meaning that they are able to produce the enzymes necessary for their mobilization, or non-autonomous, meaning that they use enzymes produced by related autonomous elements for their mobilization. TEs can also be remains of old, active elements, which are now not mobilisable. Examples of TE landscapes are shown for 4 species (Fig. 1), illustrating the variation in the proportions of TEs in these genomes (pie chart colors). Few TE superfamilies are present in the genome of the coelacanth, while many are present in the genomes of humans and bats. It should be noted that the proportion of active elements, which are those able to be mobilised, also vary among different organisms. The genetic divergence among copies of the same element is depicted in the bar graph (Fig. 1). The closer a TE is to zero on the x-axis, the more likely it is that these elements are the active ones. Few active elements are present in the coelacanth genome, only 2 TEs have been described as mobilisable in humans (LINE1 and Alu) and several are found in the fruit fly.

In summary, the portion of the genome that is occupied by TEs, the number of different elements and the proportion of active elements are highly variable among species. The “unquiet” portion of the genome, formed by
autonomous and non-autonomous mobilisable elements, can have important biologic implications.

**The unquiet portion of the genome and how it is managed**

Transposition generates genetic variability, for example by promoting mutations in the coding or regulatory regions of genes, chromosome rearrangements, TE domestication and epigenetic alterations. TEs normally contain regulatory elements, such as promoters, enhancers, cis-regulatory sequences, insulators, splice and poly(A) sites. The transposition of TEs into or close to genes can promote new regulatory patterns, and even rewire gene regulatory networks. From an evolutionary point of view, transposition can be a source of biologic innovation and TEs are important agents for the evolution of their hosts. However, for individual organisms, the majority of transpositions tend to be detrimental. Normally, the insertion of TEs into or close to a gene leads to its dysfunction, breaking a coding region or causing non-functional gene expression.

To minimise these negative effects, many mechanisms have evolved to control transposition. The 2 main strategies used to repress TE mobilization are: i) pre-transcriptional mechanisms, based on DNA methylation or the modification of histones, blocking the production of mRNA of TEs; ii) post-transcriptional mechanisms where the mRNA of TEs is selectively degraded or their translation is inhibited. These pre and post mechanisms are the first defense of organisms against the invasion of new TEs and, for the detrimental effects promoted by burst of transposition. It is done by an interaction between small non-coding RNAs and proteins of the Argonauta family. There are 3 classes of small, non-coding RNAs: i) the short interfering RNAs (siRNA) that interact with Argonauta 2 protein (AGO2) and are involved in silencing transposable elements in somatic cells; ii) the PIWI-interacting RNAs (piRNA) that are involved in the silencing of TEs in germ cells; iii) microRNAs (miRNA) that are linked to AGO1 protein and are specifically involved in mechanisms of gene regulation.

![Figure 1. TE landscapes for 4 genomes: the fruit fly, *Drosophila melanogaster*; the coelacanth, *Latimeria chalumnae*; the bat, *Myotis lucifugus*; the human, *Homo sapiens*. In the bar charts, the y-axis illustrates the percentage of the genome occupied by each TE and the x-axis illustrates the genetic divergence observed among copies of each TE. The pie charts show the proportion of the genome that is occupied by each TE superfamily. The key indicates the colors representing each TE superfamily (figure modified using data obtained from www.repeatmasker.org/genomicDatasets/RMGenomicDatasets.html).](image-url)
In contrast to the control mechanisms for TE mobilization, where the aforementioned mechanisms have been found in almost all organisms, no unified mechanism for TE activation has been found until now. This probably reflects the fact that different TEs have variable regulatory sequences and use the transcriptional machinery of cells to put them into action. Several cis-regulatory sequences have been described in TEs, for example in stress responses, inflammatory responses and other biotic stressors, developmental regulators, In summary, to be mobilised, TEs need to be activated by an endogenous factor, such as a developmental gene, or by an external source, such as biotic or abiotic stressors. Furthermore, they need to evade the TE-silencing mechanisms.

Is there a conflict for TEs between the soma and the germline?

For organisms with sexual reproduction (the majority of eukaryotes), it has been suggested that a conflict exists between the mobilization of TEs in the germline, which are those cells that produce gametes, and the somatic cells, which are the remaining cells that compose the body. Mobilization in germ cells implies that there will be an increase in TE frequency in the next generation, whereas this would not be affected in somatic cells. Evolutionarily, a “right” rate of transposition in the germline could be a source of novelties that can be captured by natural selection. Somatic transposition, on the other hand, is lost in each generation and cannot be used by natural selection. Somatic mobilization is thought to have a high adaptive cost that is paid by the individual organisms.

Until recently, little interest was given to transposition in somatic cells, and the focus of research was on transposition in the germline or the first stages of embryo development, when transposition can be transmitted to the next generation. However, in recent years, substantial evidence has accumulated that somatic mobilization is more frequent than previously thought. Variegation can be a phenotypic manifestation of somatic mobilization. Organisms showing a variegated phenotype due to somatic mobilization are more common in laboratory strains or cultivated plants, although they can still sometimes be found in natural populations. The development of molecular tools has revealed more instances of somatic mobilization than when only phenotypic analysis was available. It is now observed in organisms as diverse as Caenorhabditis elegans, Drosophila, mice and humans. Thus, the hypothesis that TEs are mainly mobile in germ cells is not always correct. The fact that a specific TE is active in a genome may just reflect the evolutionary “momentum” of that TE in that genome. That is, if that genome has already had time to develop silencing mechanisms for the specific TE, or if the TEs are not able to “escape” that silencing system.

Biological consequences of somatic mobilization

The consequences of somatic mobilization for organisms can be adaptive, neutral or detrimental. Phenotypic plasticity is an example of an adaptive consequence of somatic transposition. In vertebrates, the V(D)J recombination system, responsible for producing a highly diverse repertoire of antibodies and T-cell receptors, was an exaptation of the transposase from a Transib element, which resulted in the
promotion of this phenotypic plasticity. Another example of somatic mobilization that can be associated with phenotypic plasticity is neuroplasticity. In humans, the LINE-1 retrotransposons contribute to neuronal diversification and plasticity. The variability produced by TE activity may play an important role in cognitive development and behavioral differences between individuals. Similar results were obtained in Drosophila, where several TEs are active in a region of the central nervous system, called mushroom bodies, which is involved in the olfactory memory. These results suggest that genomic heterogeneity is a conserved feature of the brain.

The Weismann theory of early separation between germ cells and somatic cells is not applicable to all organisms. Some invertebrates, such as corals and worms, as well as the majority of plants, lack segregation of the germline and somatic cells. In these organisms, germ cells arise continuously from somatic stem cells, and somatic mutations can be incorporated into gametes. For these organisms, as well for those that reproduce asexually, somatic mobilization is source of genetic variability that fuels evolution. Asexual reproduction is found in over half of all eukaryotic phyla and some animals are predominately clonal, such as many aphids, freshwater snails, cladocerans, platyhelmints, bryozoans and corals. Somatic variation can contribute significantly to the adaptive capacity of long-lived organisms such as trees, increasing the ability of plants to colonise or persist in variable environments, and mosaicism can be a way of responding to plant-herbivore interactions.

Some somatic transposition can be neutral, when the insertion in the genome occurs in a location that does not promote functional consequences. The recent possibility of assembling genomes of single cells has revealed that, in general, metazoan individuals are complex mosaics of genetically distinct cells. The mosaicism can be so extensive that, in some cases, each cell in an organism has an exclusive genome. This research has revealed a hidden mosaicism not previously imagined. The role played by TEs in this mosaicism is yet unknown, but as somatic mobilization is observed in various organisms, it is expected that somatic mobilizations could be a part of the generation of mosaicism.

For those organisms that undergo separation of germline and somatic cells, the ontological phase in which the somatic mobilization occurs can be important in the final mosaic phenotype (Fig. 4). If it occurs early in embryogenesis, large areas of the body will show the alterations, whereas if it occurs later, the areas will be small. For neutral alterations this does not matter, but for detrimental insertions it can be significant.

Somatic transposition also has many negative effects on host organisms. TEs can produce mutations, breaks in the DNA molecule and epigenetic or chromosomal changes, which contribute to genome instability. These processes when occurring in somatic tissues can be related to the development of various diseases, such as psychiatric disorders, neurodegenerative diseases and cancer. For example, abnormal activity of retrotransposons has been detected in the brains of patients with schizophrenia.
bipolar disorder, autism and severe depression. Some studies suggest that the somatic mutations caused by TEs can affect the gene expression of neurotransmitters such as dopamine, serotonin and glutamate. Variation in the biosynthesis of these compounds could affect the nervous system metabolism, leading to neurologic disorders. Another important factor to be considered is the neuronal death caused by the transposition of TEs into genes essential for cell function. Mutations in these genes could lead to neuronal loss in brain regions with high TE activity.

Several studies have linked the somatic mobilization of retrotransposons to cancer. Lee et al. found 190 events of somatic transposition in samples of prostate, ovarian and colorectal tumors, where TEs had inserted into tumor-suppressor genes and changed their expression. Tubio et al. analyzed 244 genomes of patients with cancer and found that 53% displayed somatic retrotranspositions. More importantly, they showed that 24% of insertions had a 3' transduction, meaning that there was occasional mobilization by the L1 retrotransposon of neighboring, non-repetitive sequences of TE. However, an open question is whether somatic transposition could be the cause of some cancers or a consequence of a neoplastic process. DNA hypomethylation seems to be very common in cancer and it can be related to the activation of TEs, increasing somatic transposition. In this way, somatic mosaicism could be a consequence of cancer and not its cause.

TE activation in somatic tissues can be involved in aging, as the genetic instability generated by TEs can be an important agent in senescence. Several hypotheses have tried to explain the genetic and environmental factors involved in cellular aging. These processes appear to be directly related to the accumulation of mutations, which results in cell death or dysfunction. Some regulatory pathways and essential cellular processes are affected during senescence. The epigenetic regulatory mechanisms seem to undergo large alterations, such as the loss of methylated regions and histone modifications. The hypomethylation of DNA can drastically affect cellular homeostasis, activating genes that previously had their transcription repressed and TEs that were silenced.

Figure 4. The ontological phase of transposition events and their effects on mosaicism (different colors). A) Transposition occurring during embryogenesis results in mutations in large areas of the body (red), while transposition occurring posteriorly results in small-area mutations (green). B) Transposition occurring during all life stages results in mosaicism with different sizes of mosaic areas.
Studies relating the decline of heterochromatin to the activation of TEs during aging have been performed in different models, such as Caenorhabditis elegans, Drosophila melanogaster, mice and the cell cultures of other mammals. In Drosophila, the reduction of heterochromatin and the activation of somatic transposition of retrotransposons were detected in body fat and this high transposition rate was correlated with the breaking of DNA molecules in this tissue. Moreover, the activation of TEs in Drosophila brains during aging and the increase in somatic transposition seem to be related to the neuronal decline of older flies. These neurologic effects can be observed early in mutant flies for the Ago2 gene, which is involved in TE-silencing in somatic tissues. These flies present a decrease in life expectancy, indicating that the activation of somatic transposition is related to a reduction in longevity. In mammals, alterations in the epigenetic pattern of heterochromatin have also been observed, leading to the somatic expression of retrotransposons in cell cultures of fibroblasts, as well as in mouse tissues in vivo. Another study examined the methylation of retrotransposons in blood cells of patients in different age groups. A significant correlation between Alu retroelement hypomethylation and aging was detected in patients between 34 and 68 y old. As has been highlighted for cancer, it is currently not clear whether somatic transposition can seen as an additional cause of aging or a consequence of aging for the disruption of silencing mechanisms of TEs. The development of new methodologies for studying somatic transposition may help in understanding the factors and mechanisms involved in aging and the diseases associated with this process, such as cancer, in addition to clarifying the participation of TEs in these phenomena.

**Perspectives**

New methodologies have allowed the determination of the genomes of single cells, as well as their gene expression, epigenetic status, and chromatin organization. Some results of these approaches reveal that somatic transposition is more frequent and relevant than previously thought. However, the biologic effect of somatic mobilization seems to be variable for different organisms, such as between those organisms for which the germline and somatic cells are separated early in development and those for which this separation does not occur at all. More research is need to verify the importance of the somatic mobilization of TEs as a source of genetic variability for organisms that reproduce asexually or that do not show separation between germline and somatic cells. For organisms showing a clear separation between the germ and soma, new avenues are opening regarding the potential of somatic transposition in promoting phenotypic plasticity, such as in the central nervous system, and its role in diseases such as psychiatric disorders and cancer, or in processes such as aging.

**Abbreviations**

Alu family of human TEs, classified as short interspersed nuclear elements (SINEs)
hAT superfamily of class II transposable element
LINE1 long interspersed nuclear elements 1, non-LTR retrotransposons
miRNA microRNAs
piRNA PIWI-interacting RNAs
siRNA short interfering RNAs
TE transposable element

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No potential conflicts of interest were disclosed.

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