The role of transposable elements activity in aging and their possible involvement in laminopathic diseases

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Highlights

- **Heterochromatin loss during aging induces a dysregulation of transposable elements.**
- **Activation of transposable elements can produce genome instability and activation of inflammatory responses.**
- **B-type lamin reduction during *Drosophila* aging is associated to transposable element dysregulation.**
- **lamin A/C depletion is associated with the activation of the *LINE-1* retrotransposon in human cells.**

Abstract

Eukaryotic genomes contain a large number of transposable elements, part of which are still active and able to transpose in the host genome. Mobile element activation is repressed to avoid deleterious effects, such as gene mutation or chromosome rearrangements. Control of transposable elements includes a variety of mechanisms comprising silencing pathways, which are based on the production of small non-coding RNAs. Silencing can occur either through transposable element RNA degradation or through the targeting of DNA sequences by heterochromatin formation and consequent transcriptional inhibition. Since the important role of the heterochromatin silencing, the gradual loss of heterochromatin marks in constitutive heterochromatin regions during the aging process promotes derepression of transposable elements, which is considered a cause of the progressive increase in genomic instability and of the activation of inflammatory responses. This review provides an overview of the effects of heterochromatin loss on the activity of transposable elements during the aging process and the possible impact on genome function. In this context, we discuss the possible role of the nuclear lamina, a major player in heterochromatin dynamics, in the regulation of transposable element activity and potential implications in laminopathic diseases.

Keywords

Transposons; Ageing; Laminopathies; Lamins; DNA damage; Sterile inflammation

1 INTRODUCTION

Transposable elements (TEs) are mobile genetic elements able to change their position within a genome, often resulting in a duplication of their sequences. There are two main classes of these genetic elements: DNA transposons, which encode a transposase required for a cut-and-paste mechanism of transposition, and retrotransposons, which transpose by reverse transcription of an RNA intermediate. Mobilization of TEs may have deleterious effects on genomes, such as the induction of chromosome rearrangements and, when inserted in the coding region of a gene, the destruction or alteration of the normal gene functions. For this reason, TEs are normally repressed by specific silencing mechanisms guided by small non-coding RNAs (sncRNAs), such as PIWI–interacting RNAs (piRNAs) and endogenous-small interfering RNAs (endo-siRNAs), which have sequence homology with the target sequences (Saito and Siomi, 2010). piRNAs, a specific class of 24- to 30-nt-long RNAs produced by a Dicer-independent pathway, are mainly active in the gonads of Metazoa (Saito et al., 2006), even if they have also been found in somatic tissues outside the gonads (Jones et al., 2016, Perrat et al., 2013). Endo-siRNAs derive from a Dicer-2 dependent pathway through the processing of endogenous double-stranded RNAs (dsRNAs) and are found both in somatic tissues and in gonads (Chung et al., 2008, Czech et al., 2008). It is known that piRNAs and endo-siRNAs targeting active TEs originate from TE sequences themselves. In fact, it has been found that most of the *Drosophila* TE-specific piRNAs and endo-siRNAs map in genomic clusters, which are rich in transposon fragments (Brennecke et al., 2007, Ghildiyal et al., 2008, Hirakata and Siomi, 2016). Clusters are transcribed and the non-coding transcripts are then processed to produce mature sncRNAs that guide specific silencing complexes to target TE sequences. In *Drosophila*, these clusters mainly localize in pericentromeric and telomeric heterochromatin, with only few of them mapping in euchromatic regions (Brennecke et al., 2007), while mouse clusters are found in gene- and repeat-poor regions (Girard et al., 2006). piRNA clusters of *Drosophila* show characteristics of heterochromatin, such as enrichment of the H3K9me3 mark and HP1 that seem to be necessary to promote the processing of the transcribed cluster sequences into piRNAs (Klattenhoff et al., 2009, Rangan et al., 2011). It has also been demonstrated that the maternal inheritance of piRNAs provides the trigger for the activation of substrates for piRNA biogenesis by inducing a chromatin environment that promotes piRNA precursor synthesis and their processing (de Vanssay et al., 2012, Le Thomas et al., 2014).

Beyond the deleterious effects, TEs have an important impact on genome-wide gene regulation. In fact, TEs and TE-derived sequences represent a consistent part of the genome of eukaryotic cells and comprise about 46% of the human genome and up to 90% of the maize genome. TE-derived sequences act as transcriptional regulatory regions in a substantial proportion of human genes, contributing to determining the regulation of the controlled genes (Bourque, 2009, Feschotte, 2008, Jordan et al., 2003, Rayan et al., 2016, Rebollo et al., 2012). In fact, there is clear evidence that regulatory regions of TEs in mammalian cells have been domesticated to modulate the regulation of nearby genes (Bejerano et al., 2006, Jacques et al., 2013, Santangelo et al., 2007). This is not a general phenomenon, since the deleterious effect of TE mobilization, but time to time host cells were able to take advantage of the consequence of new insertion events. In fact, transposition of TEs can deposit regulatory sequences across the genome, modifying the regulation of genes located nearby. Some of these events seem to have had evolutionary advantages. In addition to the role of shaping the landscape of the genome, TE sequences may also affect epigenetic regulation of host genes. Silencing of TEs can occur either through degradation of TE transcript, named post-transcriptional gene silencing (PTGS) or through repression of transcription, named transcriptional gene silencing (TGS). While

PTGS leads to the cleavage of the TE transcripts, TGS inhibits RNA synthesis through DNA methylation, and through histone post-translational modifications. TEs located in euchromatic regions of *Drosophila* are responsible for the enrichment of repressive marks in TE flanking regions, and can negatively impact the expression of neighboring genes (Lee, 2015, Lee and Karpen, 2017, Sienski et al., 2012). Gene regulation can also be influenced by the sncRNAs that originate from the processing of RNA molecules derived from TEs sequences by targeting specific mRNAs. Several reports support the hypothesis that piRNAs are involved in RNA regulation in diverse cellular processes (McCue and Slotkin, 2012, Sarkar et al., 2017, Simonelig, 2014). An interesting example is the regulation of the *nanos* mRNA decay by two TE-derived piRNAs, which is indispensable for the correct anterior-posterior axis formation during the early *Drosophila* embryo development (Rouget et al., 2010).

Given the impact that TE sequences have on the genome, any variation in the regulation of these elements can have a profound influence on the genome function.

2 THE EFFECT OF AGING ON TRANSPOSABLE ELEMENT ACTIVITY AND THE POSSIBLE CONSEQUENCES ON GENOME STABILITY AND GENE REGULATION

The transposon theory of aging proposed that the increased activation of TEs in somatic tissues during the aging process leads to a shortening of the lifespan (Driver and McKechnie, 1992). Activation of TEs is a consequence of the loss of repressive structure that occurs gradually with aging in constitutive heterochromatin regions (Driver and McKechnie, 1992, Villeponteau, 1997, Wood and Helfand, 2013). Since TEs are highly enriched in these domains, loss of heterochromatin induces an increase in TE expression and a consequent increase in transposition rate (De Cecco et al., 2013a, De Cecco et al., 2013b, Li et al., 2013, Sedivy et al., 2013). Decreased repression in heterochromatic compartments during aging has been confirmed by the higher expression levels of satellite sequences (De Cecco et al., 2013b) and of genes located within heterochromatic domains (Wood et al., 2016). Relation between activation of TEs and aging has also been supported by a study performed in termites that reveals how reproducing queens and kings can live for decades without showing significant increase in TE expression levels while major workers, which have a lifespan of few weeks, show upregulation of TEs upon aging (Elsner et al., 2018). However, while there are different studies that confirm the upregulation in the expression of TEs during aging, it is not clear to which extent this activation is associated to production of *de novo* TE mutations in somatic tissues. Using a *gypsy-TRAP* reporter system to detect *de novo gypsy* retrotransposon insertion in somatic tissues of *Drosophila*, two studies confirmed new *gypsy* integration events during aging (Li et al., 2013, Wood et al., 2016). On the other hand, another study concluded that transposition in somatic tissues is less prevalent than imagined (Treiber and Waddell, 2017). The authors of this study have shown that the idea of the accumulation of de novo TE insertions in older flies likely stems from unavoidable chimeric artefacts. In fact, starting from the assumption that exons should not be mobile, they found that the mobilization rate of exons was similar to that found for TEs. They concluded that there is a flaw in the experimental approaches that has been previously used to detect and evaluate rare somatic transposon insertions, suggesting that other studies will be necessary to understand to what extent *de novo* TE integration events take place in somatic tissues during aging. Similar considerations have been reported by Evrony et al. in a study evaluating somatic *LINE-1* retrotransposition events in hippocampus and cerebral cortex by single-cell sequencing and bioinformatics analysis (Evrony et al., 2016). Chimeric artifacts were find, deriving from DNA fragment connecting *LINE-1* sequences to an unrelated portion of the genome. They confirmed *LINE-1* mobilization but with a rate which is about fifty-fold lower than previously reported. To date, the estimated *LINE-1* mobilization rate during mammal brain development vary considerably (Faulkner and Garcia-Perez, 2017, Faulkner and Billon, 2018), leaving the discussion open. The same considerations apply to the aging cell, leaving also open the question of the deleterious effect of TE mobilization during aging. However, it is

possible that the contribution of TEs to aging does not depend only on the production of *de novo* mutations. In fact, activation of *LINE-1* retrotransposons leads to a high level of DNA double-strand breaks (DSB), while the predicted numbers of successful retrotransposition events appears lower (Gasior et al., 2006). Since DNA damage is considered a cause of aging (Best, 2009, Li et al., 2008, Maslov and Vijg, 2009), the mechanism by which *LINE-1* contributes to aging could depend on the significant degree of inefficiency in the *LINE-1* integration process, which, however, produces a progressive increase of DSBs. Given these findings, *LINE-1* element activation during the lifetime in somatic tissues has been considered a possible key factor in human aging (St Laurent et al., 2010). The *LINE-1* element is also found derepressed during cellular senescence, and its upregulation activates the type-I interferon (IFN-I) response. Activation of IFN-I response seems to depend on cytoplasmic accumulation of *LINE-1* cDNA, which promotes a sterile inflammation that is a hallmark of ageing (De Cecco et al., 2019).

Expression of 111 annotated *Drosophila* retrotransposons was analyzed by RNA-seq in the fat body from young (5 days) and old (50 days) flies, finding out that 18 of them were significantly upregulated upon ageing (Chen et al., 2016). Fourteen of these TEs were long terminal repeat (LTR) retrotransposons while four were non-LTR retrotransposons. An increase of DNA damage was also found comparing nuclei of old flies with that of young ones, suggesting a causal relation between TE activation and DNA damage. They also found 18 down-regulated retrotransposons upon aging. Silencing of a number of TEs upon aging has never been reported in previous studies. While loss of heterochromatin easily explains the activation of TEs localized in heterochromatic regions, it does not explain why some TEs become repressed. However, since not all TEs map in constitutive heterochromatic regions, it is possible that the different TE regulation during aging depends on their genomic localization. It is possible that a number of TEs are repressed during the lifespan because they are located in regions that become heterochromatic upon ageing. It is also plausible that TE themselves located in euchromatic regions promote ectopic formation of heterochromatin that spreads in the surrounding genomic regions. However, another possibility to explain the silencing of some TEs during aging is that they are downregulated at posttranscriptional level. A TE co-suppression mechanism that takes place without enrichment of the repressive epigenetic marks H3K4me3 and H3K27me3 has been described for the silencing of *gypsy* (Guida et al., 2016). The appearance of de novo *gypsy* integrations in euchromatic regions determines the silencing of *gypsy* and of *gypsy* homologous sequences. This mechanism would be compatible with a general derepression of TEs induced by a global reduction of heterochromatin marks.

Summarizing all the above considerations: (I) Decrease in constitutive heterochromatin found during the aging process explains the activation of TEs observed in different species. (II) TE derepression can increase DNA damage, not necessarily inducing successful transposition events. (III) Cytoplasmic accumulation of retrotransposon-derived cDNAs can promote sterile inflammation. (IV) Silencing of a number of TEs during lifespan could have some role in the epigenetic regulation of the host genes, contributing to the deleterious effects of aging.

3 LAMINS IN THE REGULATION OF TRANSPOSABLE ELEMENT ACTIVITY AND IMPLICATIONS IN LAMINOPATHIES

The nuclear lamina is a fibrillar network that lies on the surface of the inner nuclear membrane and regulates important cellular events such as maintenance of nuclear shape, organization of heterochromatin, anchorage of nuclear pore complexes and regulation of transcription factors (Stancheva and Schirmer, 2014). The nuclear lamina consists of two types of components, lamins and lamina-associated proteins. Lamins are type V intermediate filaments and can in turn be divided into A type and B type lamins. lamin A and lamin B are necessary for maintaining heterochromatin at the nuclear periphery, though lamin A localizes also in the

nucleoplasm (Lemaitre and Bickmore, 2015). During the differentiation process, some genes interacting with the nuclear lamina are repressed while other genes that move away from the nuclear lamina can be activated (Peric-Hupkes et al., 2010). In fact, it has been reported that the ablation of the *Drosophila* B-type lamin in female somatic tissues leads to detachment from the nuclear lamina of testis-specific gene clusters and their transcriptional activation, (Shevelyov et al., 2009). All these data support the hypothesis that lamins are important to keep genes in a silent state.

Age-associated B-type lamin reduction in the fat body of *Drosophila* has been described, suggesting a possible involvement of this lamin in the derepression of TEs (Chen et al., 2016, Chen et al., 2014). Reduction of B-type lamin upon aging has been correlated with a reduction in heterochromatin and derepression of a large number of immune responsive genes (Chen et al., 2014). A relationship between age-associated B-type lamin reduction and activation of different retrotransposons has been demonstrated by the ablation of B-type lamin. In fact, both larval and young adult fat body depleted of B-type lamin show a reduction in heterochromatin at specific retrotransposon sequences and a corresponding increased expression of those TEs (Chen et al., 2016). These data support the hypothesis that the derepression of TEs observed in *Drosophila* somatic tissues during aging can be due to the reduction of B-type lamin observed during the lifespan. It is interesting to note that an age-related reduction of lamin B1 has been found in epidermal keratinocytes (Dreesen et al., 2013), in thymic epithelial cells (Yue, 2017) and in senescent fibroblasts (Shah et al., 2013) . However, also increase of *LMNB1* expression has been linked to senescence (Barascu et al., 2012, Dreesen et al., 2013), suggesting a complex mechanism of protein level fluctuation during ageing. Moreover, a major role in the ageing process is played by prelamin A, the protein precursors of lamin A or by its aberrantly spliced form called progerin. Accumulation of toxic levels of wild-type prelamin A as well as progerin expression are directly associated with cellular senescence and organism ageing (Columbaro et al., 2005b, Cenni et al., 2018), while subtoxic levels of prelamin A are found in response to stress and during physiological ageing (Lattanzi et al., 2014, Mattioli et al., 2019, Mattioli et al., 2018). All these observations suggest that changes in levels of lamin A and prelamin A could be crucial for aging.

Mutations in *LMNA* can cause a group of human diseases collectively known as laminopathies (Worman and Bonne, 2007). Hutchinson-Gilford progeria syndrome (HGPS) is an extremely rare form of laminopathy characterized by premature rapid ageing shortly after birth. This syndrome is caused by the silent mutation G608G of lamin A gene, creating a cryptic splice site within exon 11 that causes deletion of 50 aminoacids including a proteolytic cleavage site (Eriksson et al., 2003). The resulting protein, a farnesylated prelamin A form called progerin, produces nuclear lamina abnormalities and alterations in the chromatin architecture. A growing number of findings support the hypothesis that HGPS and other progeroid laminopathies may recapitulate aspects of accelerated aging (Aliper et al., 2015, Cenni et al., 2018, Gargiuli et al., 2018), suggesting that the study of these genetic diseases can shed light on the mechanisms underlying the physiological aging process. Nothing is known about the behavior of TEs in HGPS cells, and the investigation of TE regulation in these cells could be useful to looking for new evidence on the role of mobile elements in aging. As in natural aging, progeroid cells show a reduction of perinuclear heterochromatin and an increase of cell senescence, two conditions that have been correlated with a dysregulation of TEs. Similar features are also shown by cells from other laminopathic diseases, such as Emery-Dreifuss muscular dystrophy and others (Camozzi et al., 2014), making cells from these genetic disorders a tool to investigate a possible role of lamins in the silencing of TEs. If a role of lamins in the regulation of TEs is established, it will be of interest to investigate if this phenomena is correlated to some features of these complex diseases. In this respect, it is worth mentioning that Barrirer to Autointegration Factor (BAF), one of the major lamin, prelamin A and progerin partners at the interface with heterochromatin (Capanni et al., 2012, Loi et al., 2016, Samson et al., 2018), is able to protect two TEs, *Sleeping Beauty* and *piggyback*, from self-disruptive autointegration in cells that are different from their original hosts (Wang et al., 2014). Furthermore, a recent study supports a direct involvement of lamin A/C in

the repression of *LINE-1* elements (Vazquez et al., 2019). In fact, it is reported that the deacetylation of H3K18 mediated by SIRT7 is necessary to recruit *LINE-1* to the nuclear periphery, promoting its association with lamin A/C and the consequent transcriptional silencing. It was also found that depletion of lamin A/C results in transcriptional upregulation of *LINE-1* expression. This finding is in agreement with the hypothesis of the involvement of the nuclear lamina and of the lamin A/C protein in controlling the regulation of TEs.

CONCLUSIONS

TEs are important in genome function and constitute a source of genetic and epigenetic variation. However, their presence may have deleterious effects as, for example, during the aging process when TEs are dysregulated because of a progressive global heterochromatin loss. Induction of insertional mutations, DNA damage, epigenetic modifications, and stimulation of inflammatory responses are possible factors contributing to the aging process. Modifications in the nuclear lamina structure determine heterochromatin loss or detachment from the nuclear periphery as well as altered chromatin dynamics upon stress stimuli, as demonstrated in laminopathic cells and tissues (Columbaro et al., 2005a, Filesi et al., 2005, Camozzi et al., 2014, Mattioli et al., 2018). We believe that investigating laminopathic cellular models will shed further light on potential lamin A/C involvement in TE regulation and contribute to solve the puzzling issue of the pathogenetic significance of chromatin remodeling in aging and laminopathic diseases. Further, it is worth exploring the potential involvement of TE regulation in the phenotype variability observed muscular laminopathies.

Competing interests

The authors declare that there are not conflicts of interests.

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