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Altering genomic integrity: heavy metal exposure promotes trans-posable element-mediated damage

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Abstract

Maintenance of genomic integrity is critical for cellular homeostasis and survival. The active transposable elements (TEs) composed primarily of three mobile element lineages LINE-1, Alu, and SVA comprise approximately 30% of the mass of the human genome. For the past two decades, studies have shown that TEs significantly contribute to genetic instability and that TE-caused damages are associated with genetic diseases and cancer. Different environmental exposures, including several heavy metals, influence how TEs interact with its host genome increasing their negative impact. This mini-review provides some basic knowledge on TEs, their contribution to disease and an overview of the current knowledge on how heavy metals influence TE-mediated damage.

Keywords

Transposable Element; Retroelement; heavy metals; genetic damage

Introduction

Transposable elements (TEs) are mobile repetitive sequences that are universally present in most, if not all, eukaryotic organisms studied to date. The power and impact that TEs have on genomes has been known for years since their first description by Barbara McClintock [1]. Information obtained from large-scale genome sequencing has demonstrated the enormous impact of TEs on the evolution and stability of genomes. TEs make up large fractions of mammalian genomes, including at least 45% of the human genome [2], 37.5% of the mouse genome [3], and 41% of the dog genome [4]. Once considered ‘junk DNA’, transposable elements recently gained a more prominent status as several studies suggested their involvement in cell functions and gene remodeling [5]. TEs have been a major force in

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Compliance with Ethical Standards

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shaping the primate genome (reviewed in [6]) and their insertions continue to cause approximately one in a thousand new human genetic diseases [7]. In addition, once inserted, TE sequences affect gene architecture by altering expression, promoting exonization through alternate splicing, as well as serving as "nuclei" for unequal homologous recombination. Thus, mobile elements represent an important intrinsic factor contributing to genetic instability in both germ-line and somatic cells [8]. Furthermore, recent studies demonstrate that their somatic activity may play an important role in some cancers [9,10]. Data from ongoing research demonstrate that TEs respond to environmental factors. This suggests that TEs may serve as a potential link between environmental exposures and disease.

Heavy metals pose a serious threat to humans due to their abundance both in the environment and workplace. Exposure to these toxicants occurs frequently by contact with contaminated soil, water, air, and food, in addition to cigarette smoke. Chronic exposure of these toxicants can have deleterious consequences on human health. Many heavy metals, such as nickel and cadmium, are classified as carcinogens [11]. However, the exact mechanism(s) by which they induce cancer has yet to be elucidated. Multiple detailed studies support a variety of mechanisms, including (but not limited to) DNA damage through generation of reactive oxygen species [12,13], epigenetic changes [14], severe alteration of cellular homeostasis [15] and the inhibition of DNA repair pathways (*e.g.* nucleotide excision repair [16,17], non-homologous end-joining [18] and mismatch repair [19]). Most of these adverse effects likely contribute to individual aspects of heavy metal carcinogenesis, *i.e.* initiation and/or progression [20–22]. In this mini review, we explore an additional mechanism by which heavy metals can cause genetic damage. We present the current knowledge that links heavy metal exposure and increased TE-mediated damage.

Types of transposable elements

Transposable elements (TEs) or mobile genetic elements can be classified into two groups on the basis of their mode of transposition (reviewed in [23]; see Figure 1A). Class I elements, known as the "retroelements" or "retrotransposons", mobilize through an RNA-intermediate that is reverse transcribed in a "copy and paste" mechanism referred to as retrotransposition [24–26]. They are further grouped based on the presence or absence of long terminal repeats (LTRs) into LTR retroelements and non-LTR retroelements (Figure 1B). The endogenous retroviruses (ERVs or HERVs when referring to the human elements) represent the LTR retroelements. ERVs share structural similarities with retroviruses and mobilize using a comparable mechanism but maintain an intracellular existence [27]. The non-LTR elements are represented by the three currently active mobile element lineages in humans: LINE-1, Alu, and SVA (Figure 1B) [2]. Among the active families of retrotransposons in the human genome, LINE-1 represents the only autonomous lineage, possessing two open reading frames (ORFs). ORF1 encodes a 40 kDa protein with RNA-binding and nucleic acid chaperone capabilities [28]; while ORF2 encodes a 150 kDa protein possessing both endonuclease [29] and reverse transcriptase activities [30]. Both proteins are required for LINE-1 retrotransposition [31]. In contrast to LINE-1, the successful proliferation of the non-autonomous elements, Alu and SVA, depends on their ability to effectively parasitize LINE-1 proteins [32,33]. With about 1.1 million copies, the ~300 bp Alu sequence is by far the most abundant mobile element in humans comprising

roughly 11% of the genome [2]. The more recently characterized SVA element is considerably larger (~1500 bp) and has reached copy numbers of a few thousand in humans and chimpanzees [34]. LINE-1 elements, though less numerous than Alu with ~half a million copies, make up nearly 17% of the human genome due to their larger size [2]. Although a full-length LINE-1 is approximately 6 kb, most genomic copies contain truncations in varying degrees at their 5' end [35]. Sequence analyses show that the human genome harbors over 5000 full-length LINE-1s, of which about 100 are estimated to be active [36].

Class II elements, the DNA transposons, predominantly move via a “cut and paste” mechanism, exiting one locus within the genome and inserting into another without a RNA intermediate ([reviewed in [37]; Figure 1A). This class of TEs uses a transposase for their mobilization. Class II elements that encode active transposases are further subclassified as autonomous, while defective copies or non-coding elements are considered non-autonomous. During the mobilization process, transposase molecules usually bind to the inverted terminal repeats (ITRs) located within the transposon (Figure 1B) and catalyze both the DNA cleavage and strand transfer steps of the transposition reaction. As a result of the DNA cleavage, the transposase creates a double-strand break (DSB) at the excision site. Transposon integration results in the duplication of a short host sequence at the insertion site creating direct repeats (DRs), also known as target site duplications (TSDs) (Figure 1C). DNA transposons are classified into superfamilies based on sequence similarities and specific signatures in the encoded transposases [38]. Fifteen superfamilies of DNA transposons are included in Repbase: *Tc1/mariner*, hAT, *CACTA*, *P* element, *Mutator*, *piggyBac*, *PIF/Harbinger*, *Transib*, *Merlin*, *Mirage*, *Rehavkus*, *Nobosib*, *Kolobok*, *ISL2EU* and *Chapaev* [39]. A more recent analysis provides a revised classification with seventeen proposed superfamilies along 50 major eukaryotic lineages representing about 160 genomes [40]. Overall, seven of the known eukaryotic DNA transposons superfamilies are represented in humans[41] making up 3% of our genome. However, there is no evidence of current activity of DNA transposons in humans [41].

Impact of transposable elements

The ultimate role of transposable elements in the genome, or lack there-of, remains controversial. However, it is clear that TEs activity has significantly impacted the architecture of eukaryotic genomes and are considered to be an evolutionary force [37,42,43]. A positive aspect of TE activity is its contribution to the genetic diversity of organisms (reviewed in [44]). In addition, TE activity serves as a source of genetic material that can become functional or form a new gene, a process referred to as TE domestication.

Nevertheless, it is well established that host genomes may also suffer negative effects associated with TEs. TEs can generate harmful mutations through two fundamentally different processes. Due to their random insertion throughout the genome, TEs are efficient mutagens. New insertions can produce disease alleles by directly interrupting the sequence of genes or regulatory regions (Figure 2A). Multiple genetic diseases and somatic disruptions of genes in tumors caused by TE insertional mutagenesis have been reported and catalogued [9,45].

The second method by which TEs contribute to disease stems from their ability to influence the genetic environment post-insertion. Even the TEs considered as “harmless” upon insertion still retain the potential to contribute to disease through a variety of mechanisms. For example, the repetitive nature of TEs favors non-allelic homologous recombination (NAHR) events due to misalignment during the DNA exchange process (Figure 2B). By promoting NAHR, TEs can contribute to either the loss or gain of genetic material. A genomic comparison between the human and chimpanzee sequences revealed the loss of over 192,000 bases in the human genome due to Alu-mediated NAHR events [46]. Interestingly, specific genes and genomic regions appear to be particularly susceptible to this form of genetic instability [8,47].

Due to the abundance of Alu sequences in the genome (about one insert every three kb), Alu-associated NAHR in germline and somatic tissue has contributed to a diversity of human diseases [7,48,49]. The first report of Alu-mediated recombination was a case of hereditary nonpolyposis colorectal cancer [50]. Since then, over twelve different types of cancer caused by NAHR between Alu repeats have been identified [48]. Some of these include Ewing sarcoma, breast, ovarian and prostate cancers, hereditary diffuse gastric cancer and the autosomal dominant familial cancer Von Hippel-Lindau (VHL) syndrome [7,51,52]. Multiple cancer-associated loci show propensity to Alu-mediated NAHR. For example, the VHL, MLL1, MLH1, MSH2, BRCA1, and BRCA2 are recurrently affected by Alu-mediated NAHR [48]. The majority of cases of acute myelogenous leukemia (with no visible translocation) involve Alu-mediated NAHR duplication events in the MLL1 gene [53]. Similarly, recurrent germline Alu-mediated NAHR in the LDLR (hypercholesterolemia), alpha-globin (alpha-thalassemia) and C1 inhibitor (angioneurotic edema) genes have also been reported [7]. The overall density of Alu elements seems to be a contributing factor for the recurrent nature of NAHR events in these genes. Estimates indicate that Alu-mediated NAHR contributes to ~0.3% of all human genetic diseases [7,54]. However, as the majority of larger genomic rearrangements are uncharacterized to this level, this estimate likely represents an underestimation. Interestingly, double-strand breaks promote NAHR particularly when it occurs within or near repeat DNA, such as TEs [55,56].

Autonomous TEs express proteins required for their retrotransposition. In some cases, the activity of these proteins negatively impacts the cell. For example, LINE-1 ORF2 expression is associated with genetic damage and/or genotoxic stress (Figure 2C). For every successful LINE-1 insertion, ORF2 endonuclease creates between 10–100 fold excess of DSBs [57]. In addition, the reverse transcriptase activity from TEs has been also implicated in neurological diseases [58] and cancer [59]. However, further studies are required to prove a causal effect.

Furthermore, TE insertions found in non-disruptive locations can influence surrounding genes. Multiple reports demonstrate that TEs influence RNA splicing, causing exonization of TE sequences [60,61] (Figure 2D). Many examples show that point mutations in Alu inserts have led to the activation of cryptic splice sites, causing genetic defects [62,63]. Growing evidence supports that many Alu elements present in genes contribute to a significant amount of alternative and aberrant splicing [64,65]. In most cases, these outcomes are expected to result in defective transcripts and would, therefore, decrease the

overall expression from those genes (Figure 2D). Thus, far from being innocuous passengers, TEs are strong drivers of genome remodeling.

Host Repression of Mobile Elements

TEs create irreversible genetic damage, driving host genomes to evolve multiple defense mechanisms that implement a wide range of inhibition and surveillance pathways to minimize their impact [66]. TE silencing is a common regulatory mechanism used by cells to control the impact of these elements. Many higher eukaryotic organisms regulate epigenetic modifications and DNA-associated histone proteins via small RNAs in order to repress TE expression [67,68]. Many investigators consider the primary function of cytosine methylation to be the repression of TE proliferation and the associated deleterious mutations [69]. Studies show that genomic demethylation activates TE expression [70,71]. DNA hypomethylation is most tightly tied to carcinogenesis potentially through the deregulation of TEs [72].

TE regulation also includes different post-transcriptional controls. Reports demonstrate that several APOBEC3 members and proteins from the nucleotide excision repair (NER) pathway inhibit LINE-1 retrotransposition. Furthermore, some controls directly regulate the post-insertional effects of TEs. For example, cells express hnRNPC and U2AF65 to protect the transcriptome from Alu-mediated exonization events [73]. As more studies focus on TE biology, new mechanisms regulating these elements are likely to be discovered.

The influence of environmental stimuli and heavy metals on TE-mediated damage

Being an intrinsic part of the human genome, TEs are a constant threat. Thus, TE-mediated damage may not be avoidable and should not be ignored. Exposure to either normal or introduced environmental stressors can impact the expression and activity of TEs in a variety of hosts [43]. Separate research groups have exploited the sensitivity of TEs to environmental toxicants to develop specific monitoring assays. In 2005, Pesheva et al introduced the Ty1 transposition assay in *Saccharomyces cerevisiae* to detect for the presence of carcinogens [74]. In addition, Terasaki et al developed an *in vitro* screen to examine L1 retrotransposition rates in the presence of different compounds [75]. The results from the studies evaluating different environmental effects on TEs are listed in Table 1.

Experimental data show that stress induces TE transcription and integration, or redirects TE integration to different insertion sites [76,77]. Insults like DNA damage [78], ionizing radiation and heavy metals [79–81] induced expression and in some instances retrotransposition of Ty1 elements in *Saccharomyces*. Similarly, expression of the oat retrotransposon OARE-1 (Ty-1 copia family) was intensively induced by wounding, UV light, jasmonic acid and salicylic acid [82]. Examples also extend to human elements. Both UV light and ionizing radiation increase the retrotransposition rates of the human LINE-1 element [83,84]. Furthermore, the circadian clock appears to regulate LINE-1 by inhibiting its activity through a melatonin-directed pathway [85].

Currently, little data exist that study the impact of heavy metal exposure on TEs. The published literature shows that TEs from various organisms respond to a variety of heavy metal exposures (Table 1). Both arsenic and hexavalent chromium increased activity of the yeast Ty1 retroelement [86]. Other examples show that in rodent cells, retrotransposition rates of the mouse LTR-retrotransposon, VL30, increased after metal exposure of arsenic and vanadium [87,88]. In addition, VL30 retrotransposition rates increased six-fold in the presence of both FeCl₂ plus H₂O₂ than with just H₂O₂ alone [89].

Previous studies from our laboratory and others have shown that human LINE-1 retrotransposition rates vary depending on the specific heavy metal evaluated. Not all types of heavy metals increase TE activity; an indication that the influence observed on TEs is unlikely the result of a generalized metal-induced stress response. LINE-1 retrotransposition increases when treated with mercury [90,91], arsenic trioxide [92], aluminum [93], cadmium [91,94] and nickel [95]. Zinc and magnesium can reverse the effects of cadmium- and nickel-driven increases in LINE-1 retrotransposition [94]. Some metals show different effects depending on the cell cycle status. For example, studies in neuroblastoma cells show that iron (Fe) and copper (Cu) only increased LINE-1 retrotransposition in dividing cells, while mercury stimulated activity in both dividing and non-dividing cells [96]. Interestingly, cobalt treatments increased LINE-1 mRNA in tissue culture experiments but retrotransposition activity remained unaffected [90,95]. Analysis of these *de novo* LINE-1 insertions revealed that cobalt increased the proportion of full-length inserts [95] further adding to the genomic load of retrotransposition-competent LINE-1s in the genome. However, most of these studies look at exposures to a single metal. Although currently unknown, the exposure to mixtures could have a compounding effect on LINE-1 retrotransposition rates. While evidence of increased retrotransposition by heavy metals has been found to be deleterious in culture, the extent of which these damaging events are occurring *in vivo* remains unknown.

As mentioned above, the repetitive and interspersed nature of TEs that populate the human genome make them prime candidates to participate in mutagenic recombination. NAHR between Alu elements generates multiple types of pathogenic genomic rearrangements [54], which are recurrently observed to cause a diverse variety of diseases [7,97] including several cancers [8]. DSBs generated in and near repetitive sequences, such as Alu elements, will promote NAHR [49,98–100]. As with DSBs caused by ionizing radiation and free radicals, we propose that heavy metals that induce DNA breaks could also initiate mutagenic recombination between TEs. The genomic damage is compounded by the fact that many heavy metals also inhibit DNA repair pathways affecting the outcome of the repair [13,101]. Thus, the concomitant ability of heavy metals to generate DNA breaks [102,103] and inhibit DNA repair provides the ideal environment for increased TE-mediated NAHR [16–18,102–105]. The genetic damage due to NAHR is irreversible with deleterious consequences. Therefore, determining the impact of heavy metal exposure on these mutagenic events is fundamental to understand the extent of heavy metal pathogenesis on human health.

Conclusion

The current knowledge and available data point towards the enhanced mutagenic potential that exists between transposable element effects and heavy metal exposure in mammalian cells. Hence the mutagenic potential of TEs in the genome could be significantly larger than previously imagined. Although there are multiple ways that metal exposure can affect TE-mediated damage, based on the current knowledge, we propose two basic mechanisms (Figure 3). The first mechanism is through the deregulation of host defense strategies that control TE activity. The ability of heavy metals to change the global methylation status (overriding host silencing of TEs) combined with its inhibitory effect on proteins such as DNA repair enzymes, provides the ideal setting for increased TE activity. For example, previous studies indicate that the NER DNA repair pathway inhibits LINE-1 retrotransposition [106]. Conversely, cadmium inhibits XPA [107,108] and XPC [108], two critical proteins required for NER. Although speculative, cadmium is likely to stimulate LINE-1 activity by interfering with the NER surveillance of this element. Similarly, the observed LINE-1 stimulation by arsenic [92] may also correlate with its ability to repress ERCC1, XPB, and XPF [109]. The second mechanism centers on the ability of heavy metals to generate reactive oxygen species (ROS) and DSBs [102,103]. Hence, heavy metal-induced DNA damage near clusters of TEs would favor repair through NAHR contributing to mutagenic changes. Although significant progress has been made, further investigation is required to determine a causal role of TEs as a fundamental mechanism by which heavy metals cause disease.

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Figure 1.

A. Classification of Transposable Elements (TEs). TEs are classified into two Class I and Class II elements. Class I elements, also known as retroelements, mobilize using an RNA intermediate that gets reverse transcribed to generate a new copy in the genome. Classes II, also known as DNA transposons, mobilize by excising itself and reinserting in a different location in the genome. **B. Schematic of basic structural organization of TEs.** A hallmark of all Class I-retroelements is the presence of target site duplications (TSD, gray arrowheads) flanking the element. The retroelements are then grouped by the presence or

absence of long terminal repeats (LTRs). In addition, the retroelements can be further sub-classified as autonomous or non-autonomous based on their ability to generate factors needed for their mobilization. The autonomous retroelements comprise the LTR-retroelements or endogenous retroviruses (ERVs) and the non-LTR retroelements also known as Long Interspersed Elements (LINEs). ERVs encode for several proteins including gag, env, and pol. LINEs may have one or two open reading frames (ORFs). Shown is a representative of the LINE-1 family with its internal promoter (PR) two ORFs and the characteristic 3' end poly-A "tail". There are several types of non-autonomous elements (Short Interspersed Elements: SINEs, SVAs and processed pseudogenes) that vary regarding their sequences composition and length. Shown is Alu an active SINE in humans. The basic components of DNA transposons are shown as a "representative" of the multiple superfamilies of Class II elements. DNA transposons are flanked by inverted terminal repeats (ITR) and direct repeats (DR, in the host-cell DNA). DNA transposons encode a transposase activity that mediates their excision and integration. Miniature inverted repeat transposable elements (MITEs) are examples non-autonomous DNA transposons.

Figure 2. Mechanisms of impact of Transposable Elements

A. Insertional Mutagenesis. Due to their random insertion, TEs affect genes by disruption or by altering genetic sequences that regulate expression or processing of transcripts. **B. Non-allelic Homologous Recombination (NAHR).** Due to their abundant nature, TEs can promote misalignment and unequal sequence exchange during recombination contributing to genetic duplications or losses. **C. Genotoxic stress.** Expression of TE-derived proteins may have activities that alter cellular processes. For example: the L1 ORF2 endonuclease activity contributes to the generation of double strand breaks (DSBs). In addition, the reverse transcriptase activity of the L1 ORF2p has also been associated with cellular toxicity. **D. Modification of normal processes.** The presence of TE sequences within genes can influence RNA processing by providing cryptic splice sites leading to the exonization of TE sequences.

A Deregulation host defenses

B Favoring TE-mediated damage

Figure 3. Potential mechanisms of metal induced TE-mediated damage

A. Deregulation of host defense mechanisms. Metals may increase TE expression through the loss of epigenetic silencing and stimulation of the TE promoters. Metals may also increase the number of TE successful insertion events as consequence of the inhibiting important proteins of DNA repair pathways or other host defense processes involved in limiting TE activity. **B. Favoring TE-mediated genetic instability.** Metals induce reactive oxygen species (ROS) that induce double strand breaks near repetitive TEs and altering

DNA repair pathway selection to promote erroneous repair such as non-allelic homologous recombination (NAHR).

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Table 1

Environmental factors affecting retroelement activity.

Factor/ compound	retroelement	Organism	Effect of exposure	References
UV radiation	Ty1	yeast	Increased RNA	[67,68]
Gamma radiation	Ty1	yeast	Increased RNA	[69]
4NQO, MMS	Ty1	yeast	Increased RNA, increased inserts in target genes	[67] [70]
UV radiation, jasmonic acid, salicylic acid	OARE-1 (Ty1-copia)	plants	Increased RNA	[71]
arsenic	Ty1	yeast	Increased inserts	[75]
Hexavalent Chromium	Ty1	yeast	Increased inserts	[75]
vanadium	VL30	rodent	Increased inserts	[77]
arsenic	VL30	rodent	Increased inserts	[76]
FeCl ₂ +H ₂ O ₂	VL30	rodent	Increased inserts	[78]
ionizing radiation	L1	human	Increased RNA, increased number of inserts	[72]
UV radiation	LINE-1	human	Increased RNA	[73]
Light, melatonin, MT1	LINE-1, Alu		Inhibits insertion	[74]
FICZ	LINE-1	human	Increased inserts	[99]
Arsenic, As ₂ O ₃	LINE-1	human (HepG2 cell line)	Increased inserts	[81]
Mercury	LINE-1	Human	Removed silencing (increased expression?) Increase inserts	[79] [80,83]
Fe	LINE-1	human	Removed silencing (increased expression?)	[85]
Copper	LINE-1	Human (HepG2 cell line)	Removed silencing (increased expression?) Less inserts	[85] [82]
Aluminum	LINE-1	human (HepG2 cell line)	Increase inserts	[82]
Cadmium, CdS, CdCl ₂	LINE-1	human	Increased inserts	[80,83,84]
Nickel, NiCl ₂	LINE-1	human	Increased inserts	[84]
Cobalt, CoCl ₂	LINE-1	human	Increased RNA, more full-length L1 inserts	[79,84]
Etoposide	Alu	human	Increased RNA, increased number of inserts	[100]