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Response of transposable elements to environmental stressors☆

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ABSTRACT

Transposable elements (TEs) comprise a group of repetitive sequences that bring positive, negative, as well as neutral effects to the host organism. Earlier considered as "junk DNA," TEs are now well-accepted driving forces of evolution and critical regulators of the expression of genetic information. Their activity is regulated by epigenetic mechanisms, including methylation of DNA and histone modifications. The loss of epigenetic control over TEs, exhibited as loss of DNA methylation and decondensation of the chromatin structure, may result in TEs reactivation, initiation of their insertional mutagenesis (retrotransposition) and has been reported in numerous human diseases, including cancer. Accumulating evidence suggests that these alterations are not the simple consequences of the disease, but often may drive the pathogenesis, as they can be detected early during disease development. Knowledge derived from the *in vitro*, *in vivo*, and epidemiological studies, clearly demonstrates that exposure to ubiquitous environmental stressors, many of which are carcinogens or suspected carcinogens, are capable of causing alterations in methylation and expression of TEs and initiate retrotransposition events. Evidence summarized in this review suggests that TEs are the sensitive endpoints for detection of effects caused by such environmental stressors, as ionizing radiation (terrestrial, space, and UV-radiation), air pollution (including particulate matter [PM]-derived and gaseous), persistent organic pollutants, and metals. Furthermore, the significance of these effects is characterized by their early appearance, persistence and presence in both, target organs and peripheral blood. Altogether, these findings suggest that TEs may potentially be introduced into safety and risk assessment and serve as biomarkers of exposure to environmental stressors. Furthermore, TEs also show significant potential to become invaluable surrogate biomarkers in clinic and possible targets for therapeutic modalities for disease treatment and prevention.

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☆ The views expressed in this manuscript do not necessarily represent those of the US Food and Drug Administration.

Abbreviations: AML, acute myeloid leukemia; BaP, Benzo[a]pyrene; CDC, Center for Disease Control and Prevention; cGy, centiGrey; COBRA, combined bisulfite restriction analysis; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DNMT1, DNA methyltransferase 1; EPA, Environmental Protection Agency; ERV, endogenous retrovirus; H3K4me3, Histone 3, Lysine 4 trimethylation; HBEC, human bronchial epithelial cells; Gy, Grey; IAP, intracysternal A particle; IARC, International Agency for Research on Cancer; IR, ionizing radiation; LET, linear energy transfer; LINE, long interspersed nucleotide element; LTR, long terminal repeat; MeV, megaelectron volt; mRNA, messenger RNA; miRNA, microRNA; MS qPCR, methylation-sensitive quantitative polymerase chain reaction; ORF, open reading frame; PAH, polycyclic aromatic hydrocarbon; PCR, polymerase chain reaction; PIWI, P-element Induced Wimpy testis; piRNA, PIWI-interacting RNA; PM, particulate matter; POP, persistent organic pollutant; RNAi, RNA interference; RUNX, runt-related transcription factor; SEPP1, Selenoprotein P1; siRNA, small interfering RNA; SINE, short interspersed nucleotide element; SOCS1, suppressor of cytokine signaling 1; SRY, sex-determining region Y; SVA, SINE-R VNTR and Alu; TE, transposable element; UTR, untranslated region; UV, ultraviolet radiation; VL30, Viral-Like 30; WHO, World Health Organization; YY1, Ying Yang 1.

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1. Introduction

1.1. Classification

Repetitive sequences account for about 40–45% of mammalian genomes, with some estimates suggesting 66–69% of the human genomes to be repetitive or repetitive elements-derived [1]. The majority of these repetitive elements are transposable elements (TEs) – repeated and mobile DNA sequences, capable of moving and invading genomes [2]. TEs are represented as retrotransposons and transposons, while the rest of repetitive elements are represented with satellite DNA and tandem repeats, which are immobile (Table 1).

TEs comprise a group of repetitive sequences that bring positive, negative, as well as neutral effects to the host organism. Previously considered as "junk DNA," it has become increasingly evident that TEs carry a set of important gene regulatory functions, including serving as recombinogenic structures for rapid genome remodeling, maintaining centromere and telomere integrity, providing alternative promoters, silencing by transcriptional or RNA interference (RNAi), and creating cryptic splice sites and polyadenylation signals [3–7]. TEs are also considered evolutionary precursors of many genes in mammalian genomes [8]. Of particular concern are the deleterious effects of TEs exerted by their transposition that may result in potential insertions and deletions within the coding sequences that may disrupt gene expression, as well as damaging recombination events [9,10].

All transposable elements can be classified into retrotransposons (or those that relocate *via* an RNA intermediate in a "copy-and-paste" mechanism, Class I) and transposons (or those that use "cut-and-paste" mechanism, Class II) (Fig. 1). Retrotransposons are clustered into Long Terminal Repeat (LTR) and non-LTR elements, depending on their structure, and can be further subdivided into autonomous (capable of propagating themselves throughout the genome) and non-autonomous (those that use machinery of other TEs). In this review, we will concentrate solely on retrotransposons, the most abundant and only active in mammalian genomes group of repetitive elements.

1.1.1. Long Interspersed Nuclear Elements (LINE)

Autonomous Long Interspersed Nuclear Elements (LINE) represent the most abundant group, not only among non-LTR retrotransposons, but of all mammalian TEs, reaching 17–23% of their genomes [6,7]. They include low-copy archaic inactive elements such as LINE-2 and LINE-3 and currently active and abundant LINE-1 (L1) elements.

Around 516,000 copies of L1 elements are present in the human genome; however, only about 100 of them are functional full-length (6 kb long) sequences. The majority of L1s are 5′-truncated (0.9 kb in length on average), incapable of retrotransposition, elements. Full length L1 contains four functional units: a ~900 bp 5′-untranslated region (UTR), a bicistronic open reading frame that encodes two proteins – ORF1p (a 40 kDa trimeric protein with RNA binding and nucleic acid chaperone activity) and ORF2p (a 150 kDa