Review Article

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Hidden magicians of genome evolution

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Transposable elements (TEs) represent genome's dynamic component, causing mutations and genetic variations. Transposable elements can invade eukaryotic genomes in a short span; these are silenced by homology-dependent gene silencing and some functional parts of silenced elements are utilized to perform novel cellular functions. However, during the past two decades, major interest has been focused on the positive contribution of these elements in the evolution of genomes. The interaction between mobile DNAs and their host genomes are quite diverse, ranging from modifications of gene structure to alterations in general genome architecture and can be regarded as hidden magicians in shaping evolution of genomes. Some of the prominent examples that impressively demonstrate the beneficial impact of TEs on host biology over evolutionary time include their role in structure and functions of eukaryotic genomes.

Key words Dynamic component - evolution - homology-dependent gene silencing - horizontal transfer - structural & functional roles - transposable elements

Introduction

Transposable elements (TEs) are discrete segments of DNA that have the ability to move from their location without a necessity of homology. Mammalian genomes are replete with both active and dead transposable elements, which can be grouped into two categories on the basis of their mobility: DNA transposons and Retrotransposons (Fig. 1). Most DNA transposons mobilize into new genomic locations without replicating while the genomic expansion of retrotransposons depends on a replicative mechanism. The original transposon is maintained and transcribed through an RNA intermediate to integrate into a new genomic location. Two broad classes of retrotransposons are identified, long terminal repeat (LTR) and a non-LTR retrotransposons[1].

During the course of evolution these elements regularly invaded from eubacteria to eubacteria, and between bacteria to eukaryotes. Being neither beneficial nor harmful to the cells, the exact nature and role of these elements are not clear. Some researchers proposed these elements to be domesticated[2] while others contend these as parasites[3]. On invasion, TEs are silenced by repressive mechanisms of transposition wherein immobilized sequences are doomed for extinction. Escape from this dead end scenario could

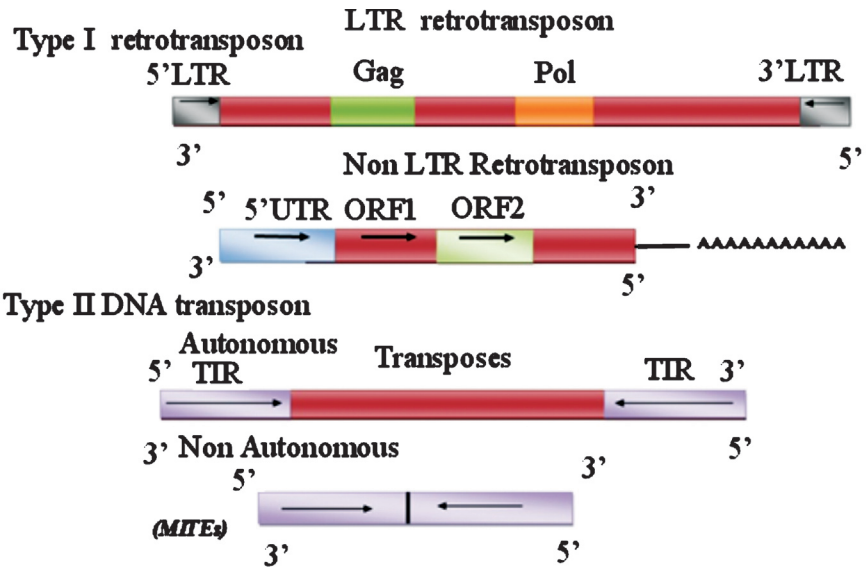

Fig. 1. Classification of eukaryotic transposable elements.

be via horizontal transfer, which later opens a new cycle of invasion of a naïve genome. It is followed by repression of the transposable elements, or recruitment of the whole or part of the transposable elements for specific function[2].

The present review focuses on the positive contributions of transposable elements in the eukaryotic genome. Invasion of TEs enhanced the evolution of genome at different strata which ranges from sequence to chromosome level. TEs contribute like hidden magicians and reshaped the architecture and functionality of the host genome.

Transposable elements in structural designing

Recent studies have shown that transposable elements play an important role in the evolution of eukaryotic chromosome structure especially the telomeres, pericentromeres and knobs, components involved in cell division and non protein coding regions of chromosomes. Recruitment of transposable elements by the host for specific structures to perform novel functions is one of the structural functions.

Genome organization: A common feature of 5' and 3' non-coding regions and introns of host plant genes enacting as miniature inverted repeat transposons *(MITEs)* is well established. Similar elements found in species as diverse as *Xenopus* (*Xenopus laevis*)[4], zebrafish *(Danio rerio)*[4], yellow fever mosquito (*Aedes aegypti*)[5], *Arabidopsis* (*Arabidopsis thaliana)*[6] and human (*Homo sapiens*) have been reported[7]. The propensity of these elements to insert into the regulatory sequences of genes suggests the possibility of their role in host regulatory evolution. In rice (*Oryza sativa*) and sorghum (*Sorghum bicolor*), matrix attachment regions (MARs) were found to co-localize with *MITEs*, suggesting that *MITEs* preferentially insert near MARs and/or serve as MARs in chromatin modelling (Fig. 2)[8].

Telomeres: Telomere is composed of repetitive DNA at the end of a chromosome, which confers protection to the terminal ends of the chromosomes. In *Drosophila* species, non-LTR retrotransposons *(HeT-A* and *TART)* accomplish this extension processes through the activity of Gag proteins in the nucleus, with the recruitment of more copies of repetitive DNA to the chromosomal ends. RNAi (RNA interference) control of *HeT-A* and *TART* was found to occur specifically in *Drosophila* ovaries and oocytes, suggesting that the transposition and subsequent chromosome elongation occur at premeiotic stages of the *Drosophila* germ line[9].

Knobs: Knobs are cytologically detectable heterochromatic components of pachytene maize chromosomes which can be identified only in somatic metaphase chromosomes by undifferential staining techniques. Fransz *et al*[10] provided a comprehensive cytogenetic analysis of a 9.5 megabase

(Mb) segment of the centromeric region and short arm of *Arabidopsis* chromosome 4, especially hk4S (Fig. 3). The hk4S knob contained multiple repeats and retrotransposon sequences. The core portion of hk4S contained 22.5 direct tandem repeats of a previously undescribed 1950 bp sequence that has certain transposon-like properties, including 31 bp direct terminal repeats with both retrotransposons and DNA transposons, as non-tandemly dispersed sequences[11].

Pericentromere: Pericentromere plays an important role in cohesin complex formation, which holds the sister chromatids together during cell division. Pericentromeric heterochromatin constituted approximately a large portion of the tomato chromosomes (*Lycopersicon esculentum*). The analysis of a 198-kb sequence near the *FER* (feline encephalitis virus-related kinase) gene, located in a distal part of pericentromeric heterochromatin on the long arm of chromosome 6 in tomato, revealed the localization of 55 transposable elements, of which 16 were novel[12].

BAC 076J21, derived from linkage group L of soybean gene, had a 102-bp tandem repeat sequences identical to a previously characterized ~120-bp repeat *(STR120)* conserved in the pericentromeric heterochromatin in all 20 chromosomes[13]. Fragments of Calypso-like retroelements, a recently inserted SIRE1 element, and a SIRE1 solo LTR were also identified within this BAC[13]. Thus presence of TEs in the genome gives rise to important structural and functional, relationship in the evolution of eukaryotic cell division.

Transposable elements in functional roles: After invasion, TEs were exploited by host genome to perform novel functions. Accumulation of TEs has created promoters and alternative promoters and raw sequences of cis-regulatory elements TFBS (Transcription factor binding sites) evolved '*de novo*' point mutations[14].

Cell cycle: The cell cycle is a universal process in which an identical copy of the genetic material is faithfully transmitted to a daughter cell. It encompasses synthesis (S) phase, which consists of DNA replication, synaptonemal complex (SC) formation, recombination and gene conversion.

Synaptonemal complex formation (SCs): Alternatively highly conserved and ubiquitous DNA sequences can be viewed as uniform structural blocks that may preferentially be recognized by proteins specialized in assembly of synaptonemal complexes. Rat genomic DNA associated with SCs is found to be enriched with repeat sequences (*L1, SINE* and *LTR* elements). Further, immuno-fluorescence *in situ* hybridization and immuno-electron microscope approaches also suggested local enrichment of *L1* and *SINE* sequences in SC, highlighting the functional role of transposable elements[15].

Replication: A helitron is A DNA transposon found In eukaryotes which replicates by a rolling-circle mechanism. Iterative Screening by PSI-BLAST showed that ATHEL 1p contains an 11-aa motif similar to the "two-His" motif conserved in the Reps encoded by a diverse set of plasmids and ssDNA viruses[16]. Most importantly, Reps perform both cleavage and ligation of DNA, reactions that initiate and terminate rolling-circle replication[16].

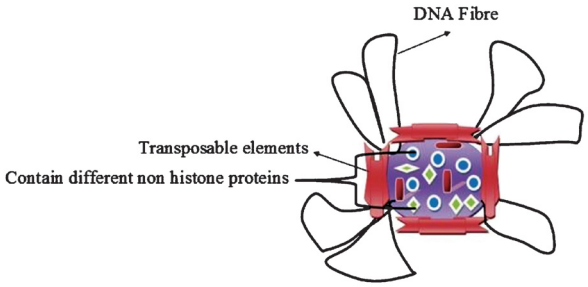

Fig. 2. Miniature inverted repeat transposons *(MITEs)* acting like scaffold or matrix associated regions on which DNA fiber form loops and creating higher order of genome packing and organization.

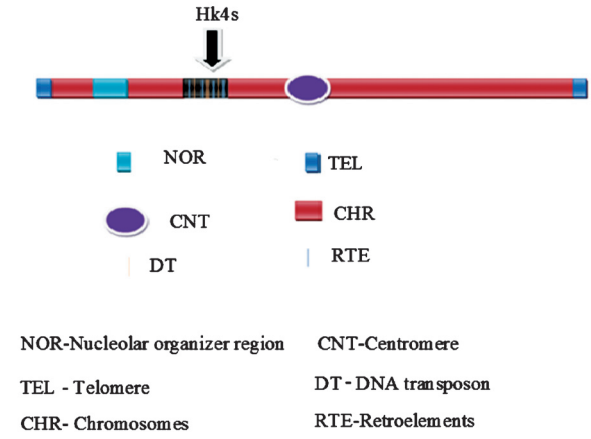

Fig 3. *Arabidopsis thaliana* chromosome knob showing presence of both retrotransposon and DNA transposon.

In *Saccharomyces cerevisiae*, a substantial fraction of the predicted origins was associated with transposable elements, which include *Ty, LTR, and tRNA* sequences. Future analyses of the functional interactions between replication origins and transposable elements may provide important insights into the regulation of origin of replication function[17].

Gene coordination: Studies have shown that TEs play a major role in the evolution of eukaryotic gene regulation.

TEs as transcriptional enhancers: The involvement of TEs in tissue-specific gene transcriptional regulation of *Hopscotch* which is inserted in a regulatory region of the maize gene, *teosinte branched1* (*tb1*). It acts as an enhancer of gene expression and partially explaines the increased apical dominance in maize when compared to the wild progenitor- *Teosinte*[18].

TEs as insulator elements: The temporal and spatial regulation of gene expression is known to be linked to the establishment of functional chromatin domains. Several lines of evidence point to retrotransposons serving *in vivo* as insulator sequences which distinguish blocks of active and transcriptionally silent chromatin (Fig. 4). According to Lynch *et al*[19] the transposable element, *MER20* acted as an insulator and reorganized a segment of ancient placental mammalian genome into active and inactive regions in the same segment, resulting in the formation of a new gene regulatory network that helped in the evolution of pregnancy in mammals.

Genetic network: Wang *et al*[20] found that a set of closely related families of *LTR* elements (class I endogenous retroviruses) dispersed 1,500 near-perfect binding sites for the 'master' regulatory factor p53. These results strongly suggest that the dispersion of the *LTR* elements promoted the assembly of a primate-specific transcriptional network of p53-regulated genes (Fig. 5).

In trypanosomatid, L. most of the protein-coding genes are co-transcribed as large polycistronic transcripts[14]. Almost all the 1,000 copies of *LmSIDER2*, an extinct family of retroposons, are located in the 3′ UTRs of predicted mRNAs and experimental introduction of a *LmSIDER2* copy in the 3' UTR of a reporter gene decreased the stability of the resulting mRNA apart from downregulation of gene expression. Together, the data support that the TE family is recruited at the whole-genome level to modulate post-transcriptional expression of hundreds of genes[14].

Transcription: One of the direct influences of transposable elements on the host genome is in the modulation of the structure and expression of "resident" genes.

Transposable element derived hypersensitive sites (HS sites): The contribution of TEs to HS sites (sequences sensitive to cleavage by DNase I and other various nucleases) in the human genome was evaluated by comparing the results of a Repeat Masker (a programs that screens DNA sequences for interspersed repeats and low complexity of DNA sequences) analysis of hg17 to the mapped locations of the National Human Genome Research Institute (NHGRI)[21]. HS sites which

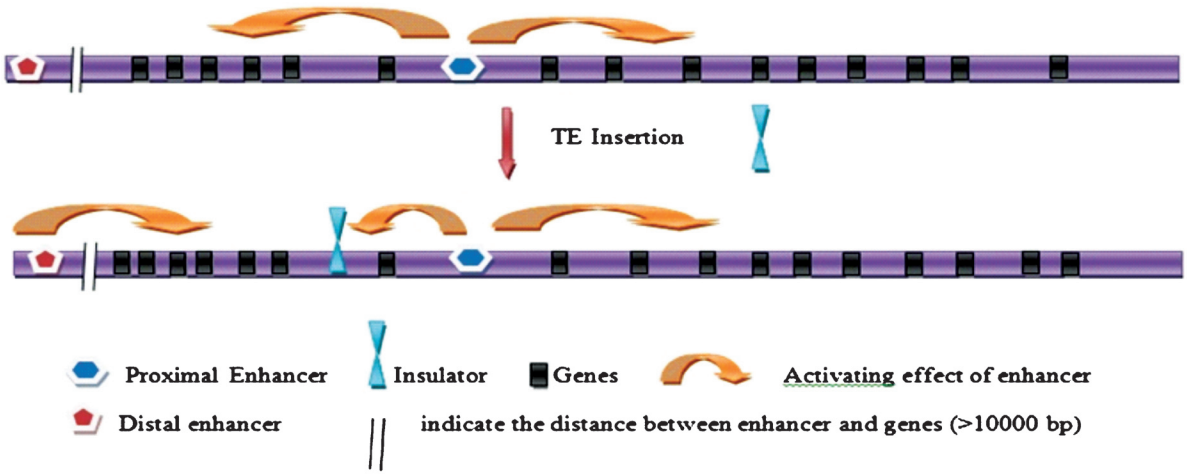

Fig. 4. Insertion of B2 SINE in between two different groups of genes leading to formation of a novel insulator boundary which leads to differential gene expression of earlier co-expressed genes.

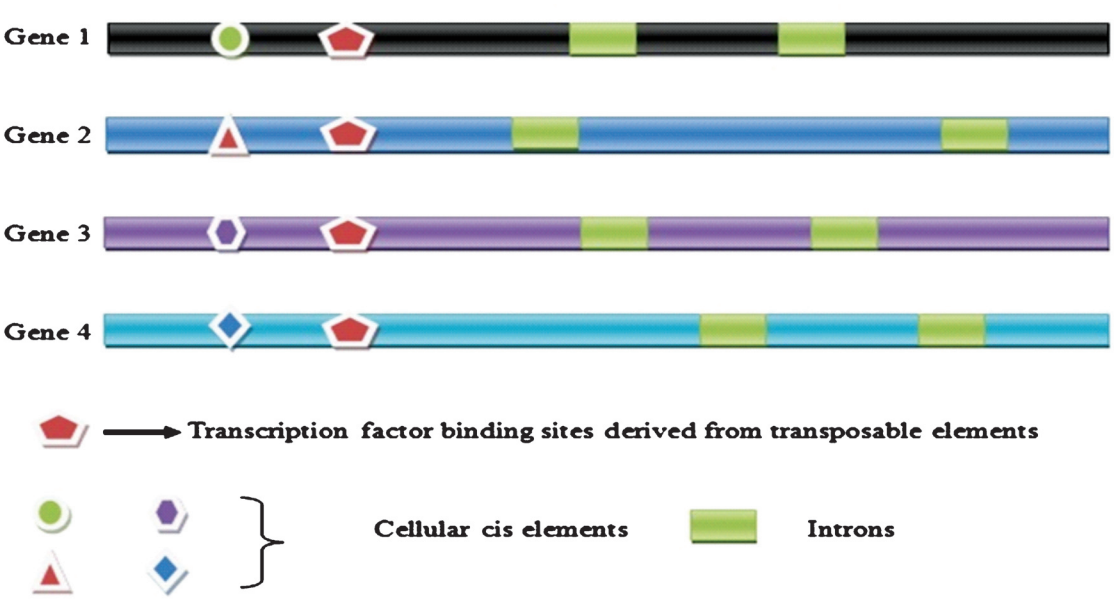

Fig. 5. Dispersion of the *LTR* elements on different regions/locus in genome created a primate-specific transcriptional network of p53-regulated genes.

revealed 3,229 HS sites (~23) derived from TEs. This substantial fraction of HS sites derived from TEs is likely to be an underestimate since some TEs have diverged beyond recognition and others may not have been covered by the RepBase library employed by RepeatMasker[21]. The analysis of gene expression data indicated that TE-derived HS sites play a functional role related to CD4+ T cell-specific gene regulation. Thus, the TE-derived HS sites may provide a specific mechanism for lineage-specific regulatory phenotypes, which in turn are important in the generation of higher level phenotypic variation between species[21].

TE sequences in promoter regions: It seems that a sizable fraction of eukaryotic, gene-associated regulatory elements is evolved by insertion of TEs. A survey in 846 functionally characterized cis-regulatory elements from 288 genes showed that 21 of these elements (2.5%) from 13 genes (4.5%) were found to reside in TE-derived sequences. The same study showed that TE derived sequences are present especially in promoter regions, located 500 bp upstream of functionally characterized transcription initiation site[22]. Another study showed that the 5' UTRs of a large proportion of mammalian mRNAs contain TE fragments, suggesting its role in regulation of gene expression[23].

TEs as alternative promoters: TEs can either influence the level of a corresponding RNA transcription or changes its expression based on tissue specificity. For example, *LTR* integration into cytochrome 19 (CY19) *CYP19* gene, encoding for aromatase P450 a key enzyme in estrogen biosynthesis, led to the formation of alternative promoter located 100 kb upstream of the coding region (Fig. 6). This event resulted in the primate specific transcription of *CYP19* in the syncytiotrophoblast layer of the placenta[24]. Placental specific transcription driven from endogenous retroviral promoters were also shown for *Midline 1 (Mid1)* gene linked with inheritable Opitz syndrome, endothelin B receptor, and insulin-like growth factor INSL4. Solitary endogenous retrovirus-like elements (*ERV-L*) *LTR* was shown to promote *b3GAL-T5* transcription 324 in various tissues, being especially active in colon, where it is responsible for the majority of gene transcripts[24]. An interesting example of gene transcriptional regulation by *LTR* was shown for neuronal apoptosis inhibitory protein *(NAIP)* gene coding for neuronal apoptosis inhibitory protein[24]. Although human and rodent *NAIP* promoter regions share no similarity, in both cases *LTR* served as an alternative promoter. Thus, two different LTR retrotransposons were shown to recruit independently in primate and rodent genomes for gene transcriptional regulation[24].

TEs derived transcription factor binding sites: Bourque *et al*[25] have shown that transcriptional regulatory networks are highly dynamic in eukaryotic genomes and that transposable elements play an important role

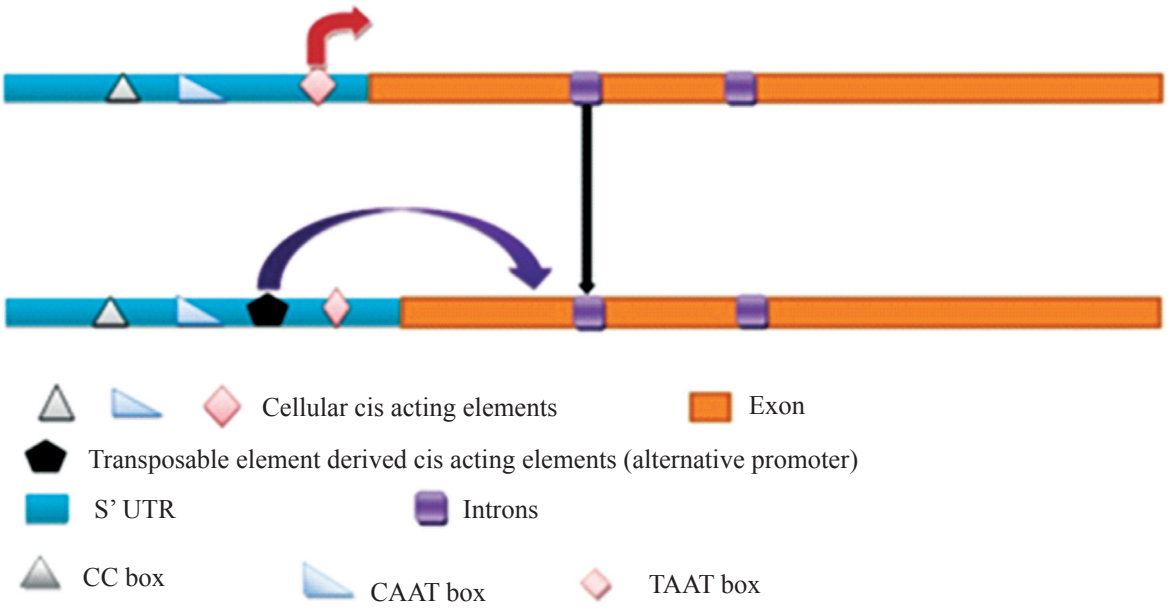

Fig. 6. *LTR* integration into *CYP19* gene in 5' UTR leads to formation of a novel alternate promoter which causes spatial and temporal gene expression.

in expanding the repertoire of binding sites. Five of the seven TFs genes [estrogen receptor 1 (*ESR1*), tumour protein 53 (*TP53*), myelocytomatosis viral oncogene homolog (*MYC*), v-relreticuloendotheliosis viral oncogen homolog A (*RELA*), POU Domain, class 5, transcription factor 1 (*POU5F1*), SRY box containing gene 2 (*SOX2*), and CCCTC-binding factor (*CTCF*)] were shown to have a significant proportion of the binding sites embedded in specific families of repeats (17.7% within *MIR* for *ESR1*, 32.1% within *ERV1* for *TP53*, 19.0% within *ERVK* for *POU5F1-SOX2*, and 28.4% within B2 for *CTCF*)[25]. Polak and Domany[26] have shown the silencing mechanism of T-cell marker gene *CD8α* by binding of lymphoid transcription factor 1 (*LYF-1*), basic helix loop helix (*bHLH*) and *GATA3* to the *Alu* sequence localized in the last intron of *CD8α*. Hence, TEs can be utilized by host to generate novel functions which can range from creation of alternative promoter to gene coordination.

Sex chromosome evolution by TEs

Y-chromosome evolution: The heterochromatic regions distributed over more than half of the human Y chromosome were found to originate ~300 million years ago (m.y.a.), and the *D. melanogaster* Y chromosome that originated 60 m.y.a., is almost entirely heterochromatic. Junk DNA accumulation on Y chromosomes has been believed to be a reason for Y-chromosome degeneration[27]. Insertion of repetitive sequences into coding genes and regulatory regions may induce alteration in the gene functions and leads to gene loss[27].

Accumulation of repetitive sequences was generally found in the evolutionarily young plant Y chromosomes. The papaya Y chromosome is the youngest of the plants, having diverged from the X chromosome only 2–3m.y.a where accumulation of repetitive sequences and heterochromatinization was detected[27].

The *D. miranda* neo-Y chromosome provides several fascinating insights into the early stages of Y-chromosome evolution. However, about one-third of the genes studied to date are clearly non functional on the neo-Y, containing frame shift mutations or premature stop codons[28]. Most remaining neo-Y genes showed more subtle changes, such as an elevated rate of amino acid substitution, an accumulation of unpreferred codons, and less evolutionary constraint in regulatory regions. Transposable elements were found to be accumulated on the neo-Y chromosome and interspersed among functional genes. This pattern strongly suggested the TEs to play an active and early role in the process of Y-chromosome degeneration. Thus, a diverse array of molecular changes, likely to represent a wide range of deleterious fitness

effects, contributed to the observed degeneration of Y-chromosomes[28]. These examples indicated that TEs have generated changes in chromosome number and structure which lead to evolution of karyotypes and eukaryotic genome.

X-Chromosome inactivation and role of TE: X chromosome inactivation helps to achieve equal expression of X-linked genes in males and females. XIC(X-Inactivation Center)[29] plays a central role in inactivation of chromosomes. Translocation of XIC in autosomes leads to silencing of autosomal genes but extends far less and reduces efficiency when compared to X-chromosome. This indicates that a certain specific sequence in X-chromosome promotes the spreading of silencing on the X chromosome.

Bailey *et al*[30] used sequence data from human genome project to compare the relative content of *L1* elements from autosomes and X chromosomes. Comparison results revealed that X chromosomes were indeed richer in *L1* elements (26%) than autosomes (13%). The density of *L1* is highest at Xq13–Xq21 and XIC maps to Xq13 indicating the central role of *L1* elements in spreading of X inactivation by acting as waystation or booster elements. The exact mechanism of heterochromatin formation is still unclear but some proteins like SATB1 which is a global chromatin organizer as well as a transcription factor, plays an important role in higher order chromatin organization and gene regulation.

The combined effort of Xist RNA, *L1* elements, SATB1 protein and other unknown factors leads to formation of heterochromatin in transcriptionally silenced X chromosome contributing to equal expression of X-linked genes in both sexes[30].

TE and origin of long non coding RNA: Recent research has revealed that long non coding RNAs (lincRNAs) comprise an essential part in genome regulation and found in diverse organisms. These play an important role in cell differentiation and disease pathways. Insertion of TEs in genome is an important source of lincRNAs origin. After insertion in lincRNAs these modify sequence, structure and regulation and create novel lincRNAs loci because of their transcription promoting nature.

A study by Kelley and Rinn[31] revealed that 127 *HERVH*- lincRNAs are clearly enriched by *HERVH LTR7* transcription activation signal in the sense orientation at the transcription start site. These lincRNAs show dramatic stem cell specific expression in both H1-hESCs (Human embryonic stem cells) and iPSCs (induced pluripotent stem cells)[31].

Table. Diseases caused by insertion of transposable elements in the genome

Locus	Chromosome	Diseases
Alu insertion		
F8	X	Haemophilia B
F9	X	Haemophilia A
CLCN5	X	Dents disease
CRB1	1	Retinal binding
ZEB2	2	Muckle wells syndrome
L1 insertion		
CHMb	X	Choroideremia
APCs	5	Colon cancer
FKTNb	9	Fukuyama-type congenital muscular dystrophy
HBBb	11	Beta-thalassaemia
SVA insertion		
BTKb	X	X-linked agammaglobulinaemia
LDLRAP1b	1	Autosomal recessive hypercholesterolaemia
SPTA1b	1	Hereditary elliptocytosis and hereditary pyropoikilocytosis
FKTNb	9	Fukuyama-type congenital muscular dystrophy

Source: Ref. 32

Conclusion

One has underestimated the structural and functional role of transposable elements in the higher organism's complex genome by assumption of TE sequences to be junk DNA. Hence, involvement of transposable elements in structural and functional sequences added further complexity to the mammalian genome. The positive role of the TEs hence requires future focus to resolve the importance of transposable elements in eukaryotic genome, which may include their role in chloroplast and mitochondrial genome.

Detailed analysis of the role of transposons in an organism and its genome organization can help one to create useful entities such as artificial chromosomes wherein minimal amount of support material can be used to incorporate huge amount of target sequences

that can be used as cloning vectors and expression systems.

Since TEs accumulate more rapidly on sex chromosomes, the insertion of retrovirus like element may have resulted in evolution of X-chromosome and X-linked diseases/disorders. Studies need to be focused to elucidate the importance of transposable elements induced genetic variation in commercially important plants and animals and their role in genome skeleton and whole genome duplication.

The role of TEs as a unifying pathogenic agent in various disorders (Table)[32] further needs to be elucidated to expand our horizon on the aetiology of disorders. This emerging area of knowledge will spur efforts to decipher the causes of unique and yet unidentified diseases/disorders. Studies exploring the role of mutations in genetically deregulated cellular processes especially in cancer and neurological diseases need to be initiated to understand the role of TEs in human disorders.

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