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Review on Type and Characteristics of Transposable Elements

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Abstract: A transposable element or jumping gene is a DNA sequence that can change its position within a genome, altering the cell's genetic character and genome size. The mobilization of transposable elements (TEs) is called transposition or retro transposition, based on the nature of the intermediate used for mobilization. Transposable elements are bits of nucleic acid that encode the inborn ability to mobilize from one genomic position to another. This ability to "jump" is facilitated by element encoded proteins such as DNA transposase or reverse transcriptase. Thus, TEs have played a key role in genome evolution. Transposable elements make up a large fraction of the genome and are responsible for much of the mass of DNA in a eukaryotic cell. Although TEs are selfish genetic elements, many are important in genome function and evolution. There are at least two classes of TEs: Class I TEs(copy and paste) or retrotransposons generally function via reverse transcription, while Class II TEs(cut and paste) or DNA transposons encode the protein transposase, which they require for insertion and excision and some of these TEs also encode other proteins. TEs can positively and negatively influence a genome.

Key words: Transponsable Element · Transposons · Retrotransposons

INTRODUCTION

Transposable elements (TEs) are defined as DNA sequences that are capable to move from one place to another in the genome. It represents a vast array of genomic sequences that have (or once had) the ability to mobilize from one location in the genome to another [1]. Transposable elements (TEs) known as "jumping genes, " move, or transpose, to different locations all the way through the genomes in which they exist in. As mobile genetic elements, TEs are both drivers of evolution and potentially harmful mutagens that may insert within gene-encoding sequences [2]. TEs have been recognized in all organisms, prokaryotic and eukaryotic and can occupy abundant proportion of a species' genome. For instance, transposable elements embrace approximately 10% of several fish species, 12 % of the C. elegans genome, 37% of the mouse genome [3], 45% of the human genome and up to > 80 % of the genome of some plants like maize. Nearly 70 years ago, Barbara McClintock laid the foundation for TE research with her initial work and discoveries in maize of what she termed "controlling elements" [4].

Mobilization of TEs is termed transposition or retro transposition, depending on the nature of the intermediary used for mobilization. TEs can positively and negatively impact a genome; for instance, TE mobilization can promote gene inactivation, modulate gene expression or induce illegitimate recombination and TEs have played crucial role in genome evolution. TEs can be considered as selfish DNA or junk DNA and the existence of these elements in a genome represents the fight between selfish DNA (to be perpetuated) and the host (to restrict the spread and its consequences). As TEs make up a large percentage of genome volume, it is hypothesized that they have participated in changes of genome size during speciation and evolution, as reported in plants, Drosophila or primates [5].

According to Lander *et al*. [6] and Boeke *et al*. [7], TEs are subdivided into two major classes defined by their mobilization intermediate. Class I TEs, also known as retrotransposons, encompass elements that move via a "copy-and-paste" mechanism involving anRNA intermediate whereas Class II TEs referred to as DNA transposons, represent Tes that mobilize by a "cut-and-paste" mechanism. DNA transposons are

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currently thought to be trans positionally inactive in most mammals and with bats being the exception [8]. However, several genes in the human genome are derived from DNA transposons [6].

Tes are able to produce various genetic alterations upon insertion as a consequence of the transposition process (insertions, excisions, duplications or translocations in the site of integration). For instance, DNA transposons can inactivate or alter the expression of genes by insertion within introns, exons or regulatory regions [9]. In addition, TEs can participate in the reorganization of a genome by the mobilization of non-transposon DNA or by acting as recombination substrates. This recombination would occur by homology between two sequences of a transposon located in the same or different chromosomes, which could be the origin for several types of chromosome alterations [10].

Indeed, TEs can participate in the loss of genomic DNA by internal deletionsor other mechanisms [11]. Transposition of these elements has been linked to over 75 human diseases including hemophilia A, breast cancer, colorectal cancer, amyotrophic lateral sclerosis and frontotemporal lobar degeneration [12]. Furthermore, TEs also potentially contribute to neurologic development as well as neurologic diseases and disorders [13]. The objective of this paper is to review transposable elements.

Mechanisms for TE-Mediated Cellular Stress: The most frequently implicated pathogenic functions of TEs result from direct mutagenic effects of newly transposed insertions. L1HS elements are entirely capable of mobilizing in vivo, creating de novo insertional mutations at a rate of about one L1HS germline insertion per 100 individuals and L1 HS machinery assist mobilization of other non-autonomous TE families, including Alu and SVA, some of which are known to be polymorphic (representing relatively recent insertion events) with estimated transposition rates of about 0.04 and 0.001 new insertions per generation, respectively [14] and an overall retro transposition rate of about 0.02 germline events per generation. L1HS can also mobilize in certain somatic tissues, with a transposition rate estimated at about 0.04–13 insertions per cell in neurons [15]. This cell-type-specific mosaicism could explain reports suggesting that de novo transposon insertions are more commonly found in brain compared to other somatic tissues and that neuronal cells are more permissive to retro transposition [16]. However, a comprehensive study comparing somatic transposition rates across healthy human tissues has not been completed. In contrast, somatic retro transposition is much more common in human cancers with an estimated rate of 4–100 de novo insertions per tumor in many tumor types of different tissues [17].

Types of Transposable Elements: Two major classes of TEs exist: Class I TEs, also called retrotransposons, utilize an RNA intermediate that is reverse transcribed before genomic reinsertion; Class II TEs, or DNA transposons, move via excision from one genomic location and insertion into another. In most genomes, Class I retrotransposons represent the vast majority of TE derived sequences since new copies accumulate with each transposition event [6].

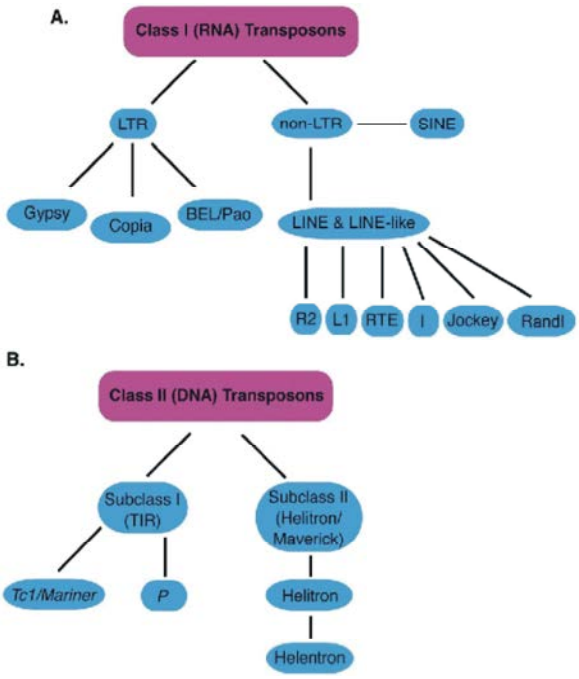

Fig. 1: [18]

Types of DNA Transposons (Class II Elements)

TIR Transposons: DNA transposons are divided into 2 sub-classes based on their transposition mechanisms. Sub-class I elements utilize the canonical cut-and-paste mechanism of TIR transposon transposition and are divided into several superfamilies': Tc1/*mariner*, PIF/*Harbinger*, hAT, Mutator, Merlin, Transib, P, *piggyBac* and CACTA. Sub-class II DNA transposons include *Helitron* and *Maverick* elements that utilize unique transposition mechanisms [19]. DNA transposons are generally regarded as "extinct" in humans and other mammals as most are non-autonomous [20].

DNA transposons, or terminal inverted repeat (TIR) transposons, consist of a transposase gene flanked by TIRs and move via a cut-and-paste mechanism. TIRs are repeating sequences found at both ends of these elements and are inverted with respect to each other. The transposase is responsible for excising the transposon and inserting it into a new location. No active DNA transposons have been identified in humans due to lack of functional transposases, but at least 16% of the DNA transposons in *D. melanogaster* are full length and potentially active, including *1360, hobo, Bari1, pogo* and *P* elements [21].

TIR Transposases have an N-terminal DNA binding domain with HTH motifs and a C-terminal DDE or DDD catalytic domain. (B) For transposition, TIR transposases (purple circles) first bind to inverted repeats (red triangles, IR) flanking the element. Bound transposases then dimerize followed by cleavage of the element from surrounding sequences (black lines) and integration into a new target site (AT) resulting in target site duplication. The *Tc1* and *Bari1*transposase proteins consist of 2 domains: An N-terminal DNA binding domain containing helix-turn-helix motifs and a highly conserved nuclear localization signal and a C-terminal catalytic domain with a DDE motif [19].The catalytic DDE motif, or DDD motif in some families of transposases, is required for the transposition of DNA transposons in sub-class I [22]. These conserved motifs also allow the import of the transposases into the nucleus to bind TIRs, forming a complex that promotes cleavage of the entire double-stranded element [19].

P Elements: *P* elements are the best-studied DNA transposons in the *D. melanogaster* genome. Full-length autonomous *P* elements are 2.9 kb in length with 31 bp TIRs and 4 exons that encode a transposase when spliced. A similar element in the human genome, THAP9, is a confirmed DNA transposon with the ability to mobilize *P* elements in both *Drosophila* and human cell lines. Like other TIR transposons, *P* elements utilize a cut-and-paste mechanism of transposition and build target site duplications upon insertion [23].*P* elements are unique, however, in their abilities to amplify themselves in *Drosophila* germline cells due to special insertion at regions of the genome that bind the origin recognition complex and function as replication origins. By transposing during S phase from replicated genomic regions to un-replicated regions, *P* elements are copied, amplifying their presence in the genome with the aid of the host DNA repair machinery [24].

Helitrons: *Helitrons* belong to a unique subclass of DNA transposons with a distinct mechanism of transposition. Unlike other DNA transposons, *Helitrons* lack TIRs and encode a DNA helicase and replicator initiator (Rep) protein with nuclease and ligase functions, resembling the machinery of rolling-circle replicons [25]. Subclass of *Helitrons* called *Helentrons*, encodes an additional apurinic-apyrimidinic endonuclease and may also mobilizenon-autonomous *Helentron*-associated interspersed elements (HINEs) [26].

Retrotransposons: Retrotransposons can be further subdivided into two subclasses: those with Long-Terminal Repeats (LTR) and those without (non-LTR). LTR elements, also known as endogenous retroviruses (ERVs), comprise ~8 % of the human genome [6]. Many of these elements lack a majority of the viral genes and exist only as single LTRs, often referred to as solo LTRs. Similar to DNA transposons, LTR elements are thought to be inactive in the human lineage, although rare polymorphic ERVs in the human population indicate that mobilization has occurred following the human-chimpanzee divergence [27].

Retrotransposons, or RNA transposons, comprise more than 30% of the human genome and are the most abundant class of TEs in the *D. melanogaster* genome [21]. Retrotransposons include LTR retrotransposons, non-LTR retrotransposons (LINEs and LINE-like elements), short interspersed nuclear elements (SINEs) and other similar TEs [28]. Both LTR and non-LTR retrotransposons use similar mechanisms of transposition and regulation. Retroviruses may also be classified as retrotransposons as they mobilize via similar mechanisms, but are additionally able to infect other cells and organisms by horizontal gene transfer. Retrotransposons are primarily characterized by the presence of *gag* and *pol* genes that may be overlapping and require frameshifting to be translated, but may also be encoded in a single fused ORF [29].

Retrotransposon genes resemble those of retroviral genomes in both structure and function and some retrotransposons contain a third gene encoding the retroviral *envelope* (*env*) protein necessary for mobilization of retroelements outside of their host cells (Kim *et al*., 2004). Many of these retrotransposons are classified as endogenous retroviruses, or errantiviruses in *Drosophila* and other insects, as they either arose from retroviruses that lost infectivity or LTR retrotransposons that acquired *env* genes from exogenous sources [30].

Types of Rna Retrotranposons (Class I)

LTR Retrotransposons: LTR retrotransposons are abundant in *Drosophila melanogaster*, as well as in humans. In *D. melanogaster*, there are 3 recognized groups of LTR retrotransposons (Gypsy, Copia and BEL/Pao), consisting of 8 clades and at least 35 families [31]. Mechanisms of transposition may vary slightly between these groups, but all contain LTRs, a feature also common to retroviruses. LTRs play a significant functional role in the mobilization of these elements. For both retrotransposons and retroviruses, LTRs interact directly with specific integrase domains for insertion into target regions of the genome. Additionally, LTRs are processed by the integrase before insertion. Joining of the LTR ends to the chromosomal DNA generates target site duplications much like those of DNA transposon insertions [32].

Retroelements are first transcribed into *gag-pol* fusion transcripts followed by translation into Gag-Pol fusion protein products, sometimes by programmed translational frameshift. Gag-Pol peptides are then rapidly cleaved into individual protein products by the retroelement encoded protease. Programmed translational frameshift occurs in many retrotransposon transcripts near the end of the *gag* ORF due to a rare codon awaiting the arrival of its corresponding Trna [33].

Non-LTR Retrotransposons: Non-LTR retrotransposons, or LINE-like elements, have been classified into over 100 families, separated into 28 clades and 6 groups: R2, L1, RTE, I, Jockey and RandI [34]. Non-LTR retrotransposons are structurally similar to LTR retrotransposons, but often lack some of the ORFs and protein domains encoded by LTR retrotransposons and do not contain LTRs at their 3' and 5' ends [35].

Characteristics of Transposable Elements

Transposable Elements Come in Many Different Forms and Shapes: Transposable elements (TEs) are DNA sequences that have the capacity to alter their position within a genome. Consequently their deep evolutionary origins and continuous diversification, TEs come in a confusing variety of forms and shapes [7]. For instance long terminal repeat (LTR) retrotransposons, integration occurs by means of a cleavage and strand-transfer reaction catalyzed by an integrase much like retroviruses and non-LTR retrotransposons, which include both long and short interspersed nuclear elements (LINEs and SINEs), chromosomal integration is tied to the reverse transcription through a process known as target-primed reverse transcription [35]. DNA transposons, are mobilized via a DNA intermediate, either directly through a 'cut-and-paste' method or, in the case of *Helitrons*, a 'peel-and-paste' replicative mechanism involving a circular DNA intermediate [36].

TEs Are Not Randomly Distributed in the Genome: The genome may be viewed as an ecosystem settled by diverse communities of TEs, which need to propagate and multiply through sophisticated interactions with each other and with other components of the cell [37]. *These* interactions encompass processes familiar to ecologists, such as parasitism, cooperation and competition [38]. At the most extreme end of the site-selection spectrum, many elements have evolved mechanisms to target specific loci where their insertions are less harmful to the host but conducive for their propagation [39].

Natural selection and genetic drift are also influential forces determining the distribution and accumulation of TEs. *Insertions* that are strongly harmful are rapidly removed from the population. Insertions that have little or no effects on genome function and host fitness may arrive at fixation according to the competence of selection and drift at removal of these insertions from the population, which differ greatly among species [40].

TEs Are an Extensive Source of Mutations and Genetic Polymorphisms: TEs occupy a significant portion of the genome of a species, with a large fraction of the DNA unique to that species. In maize, where Barbara McClintock did her seminal work an astonishing 60 to 70% of the genome is comprised of LTR retrotransposons, many of which are exceptional to this species or its close wild relatives, but the less prevalent DNA transposons are presently the most active and mutagenic [41]. involvement of TEs to genetic diversity may be underestimated, as TEs can be more active when organisms are under stress, such as in their natural surroundings, because TE insertions rarely provide an immediate fitness advantage to their host, those reaching fixation in the population do so mainly by genetic drift and are consequently eroded by point mutations that accumulate impartially [40].

TEs Are Associated with Genome Rearrangements and Unique Chromosome Features: Transposition represents a strong mechanism of genome expansion that over time is counteracted by the removal of DNA via deletion. The balance between the two processes is a major driver in the evolution of genome size in eukaryotes [40].

There Is an Intrinsic Balance Between TE Expression and Repression: To persist in evolution, TEs must strike a delicate balance between expression and repression Expression should be sufficient to promote amplification, but not so vigorous as to lead to a fitness disadvantage for the host that would offset the benefit to the TE of increased copy numbers. This balancing act may explain why TE-encoded enzymes are naturally suboptimal for transposition and why some TEs have evolved self-regulatory mechanisms controlling their own copy numbers [42].

A variety of host factors are also employed to control TE expression, which includes a variety of small RNA, chromatin and DNA modification pathways, as well as sequence-specific repressors such as the recently profiled KRAB zinc-finger proteins [43]. Another important consequence of the intrinsic expression/ repression balance is that the effects of TEs on a host can vary considerably among tissue types and stages of an organism's life cycle. From the TE's perspective, an ideal scenario is to be expressed and active in the germline, but not in the soma, where expression would gain the TE no advantage, only disadvantage [44].

Tes Are Insertional Mutagens in Both Germline and Soma: Like other species, humans contend with a contingent of currently active TEs where the intrinsic balance between expression and repression is still at play. These elements are responsible for new germline insertions that can cause genetic disease. More than 120 independent TE insertions have been associated with human disease [45]. Historically, little attention has been given to transposition in somatic cells and its consequences, because somatic transposition may be viewed as an evolutionary dead-end for the TE with no long-term consequences for the host species. Yet, there is abundant evidence that TEs are active in somatic cells in many organisms [46]. One challenge for assessing somatic activity has rested with the development of reliable single cell insertion site mapping strategies [47].

Somatic activity has also been observed in human cancers, where tumors can acquire hundreds of new L1 insertions. Host cells have evolved several mechanisms to keep TEs in check. However, as the force of natural selection begins to diminish with age and completely drops in post-reproductive life, TEs may become more active [48].

TEs Can Be Damaging in Ways That Do Not Involve Transposition: TEs are highlyrecognized for their mobility, in other words their ability to transpose to new locations. Whereas the breakage and insertion of DNA related with transposition represents anclear source of cell harm, this is not the only or may be even the most common mechanism by which TEs can be harmful to their host. Reactivated transposons harm the host in multiple ways. First, de-repression of transposon loci, including their own transcription, may interfere with transcription or processing of host mRNAs through ainnumerable of mechanisms [49].

Regulation and Control of Transposition

Overproduction Inhibition (OPI): The transposase itself can perform as a transposition inhibitor, when it go beyond a threshold concentration, transposon activity is diminished. This fact has been seen in *Tc1/mariner* elements, even though the nature of this mechanism is not clear. As it has been recommended, transposase monomers could form inactive or less active oligomers, thus decreasing the activity of the transposition process. When the copy number of these elements increases in the host genome, the production of transposase is also increased and through OPI the mobilization of the transposon is reduced [50].

Vertical Inactivation: Eventhough Tc1/*mariner* elements are widespread in nature, the vast majorities harbor multiple inactivating mutations and only a few naturally occurring elements are known to be active. It has been suggested that this is the result of selective pressure to reduce damage to the host genome. In addition, inactive elements could produce inactive transposases that would hinder the transposition of active elements, by OPI or by competition with the active transposases for TIRs. As two functional transposase molecules are required to perform transposition, inactive transposase proteins act as dominant negative inhibitors of transposition [51].

Other Mechanisms: Host can develop different mechanisms to decrease the activity of transposons. One way used by the host to silence a Tc1/*mariner* element is DNA methylation, thus preventing its transcription, or using post-transcriptional silencing mechanisms such as RNA interference [52].

CONCLUSIONS

Transposable elements represent one of several types of mobile genetic elements and found in almost all life forms and commonlyrepresent the greatest abundant and dynamic portion of genomes in almost all living organisms. TEs can be divided into two major classes

(transposons and retrotransposons) based on their mechanism of transposition and each class can be subdivided into subclasses based on the means of chromosomal incorporation which will result to have positive and negative impacts on host by genome evolution, function and disease remain a matter of strong interrogation.

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