THE GENIES OF THE GENOME: TRANSPOSABLE ELEMENTS IN EPIGENETIC REGULATION, GENOME DYNAMICS, AND DISEASE

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PREFACE

For many years, the genome was regarded as a static repository of genetic information, composed primarily of protein coding genes, regulatory regions, and stable chromosomal structures. Within this classical framework, DNA was perceived as a passive template, faithfully transmitting biological information across generations. However, rapid advances in molecular biology and genomic technologies have fundamentally reshaped this perspective. Today, the genome is understood not merely as an information archive, but as a dynamic and responsive system, characterized by internal mobility, regulatory plasticity, and continuous evolutionary interaction. Among the most striking components of this dynamic architecture are transposable elements.

Transposable elements (TEs), despite constituting nearly half of many eukaryotic genomes, were long dismissed as non-functional, repetitive, or "selfish" DNA. Their biological significance was largely underestimated. Accumulating evidence over the past decades, however, has revealed that TEs actively participate in a wide range of fundamental biological processes, including gene regulation, chromatin organization, epigenetic control, and the generation of evolutionary novelty. Rather than representing a genomic burden alone, TEs contribute substantially to genome flexibility, adaptability, and long-term evolutionary potential.

This book aims to provide a comprehensive examination of transposable elements, encompassing their historical discovery, classification, molecular mechanisms, evolutionary consequences, and interactions with environmental and epigenetic factors. The mobility of TEs within the genome, the evolutionary balance between host defense mechanisms and TE persistence, and the biological outcomes of disruptions in this balance are discussed from an integrative and interdisciplinary perspective. Particular emphasis is placed on the role of environmental stressors in modulating TE activity, highlighting transposable elements as sensitive indicators of genome environment interactions.

By approaching transposable elements not solely as sources of genomic instability or disease, but also as essential drivers of regulatory innovation and evolutionary change, this work seeks to offer a balanced and contemporary framework. Understanding these mobile genomic components often hidden within the silent regions of the genome is critical for addressing fundamental questions in genetics, epigenetics, and evolutionary biology.

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1.Transposable Element Activation and Genomic Instability

Transpositional elements (TEs) are mobile DNA sequences that can move from specific locations to other locations within the host genome and often replicate by creating copies of themselves. These elements are not only a structural component of the genome but are also considered one of the key determinants of genomic plasticity and diversity. The presence of TEs is one of the most concrete examples demonstrating that the genome exhibits a dynamic and variable organization, rather than a static structure (Wells, Feschotte, & Hancks, 2020; Fueyo, Richardson, & Faulkner, 2022; Hoyt et al., 2022).

TEs, observable in all life forms, have played a critical role in shaping host genomes throughout evolution. In mammalian genomes in particular, TEs constitute approximately 50% of the genome and are generally divided into subclasses such as LINEs (Long Interspersed Nuclear Elements), SINEs (Short Interspersed Nuclear Elements), DNA transposons, and retrotransposons. This diversity reveals that TEs not only function as genomic "glue" or repetitive sequences, but also influence many fundamental biological processes such as gene expression, chromatin structure, DNA repair, and genome stability (Wicker et al., 2007; Pace & Feschotte, 2007).

The abundance and transposition capabilities of TEs vary from organism to organism. In some species, active TEs can be transported to new locations within the genome at high frequency, while in others, TEs are largely passive and evolutionarily "fossilized." This highlights the complexity and diversity of the role TEs play in genome dynamics and evolutionary innovation. For example, active LINE-1 elements still possess retrotransposition capability in human and other mammalian genomes and are linked to gene mutations, chromosome rearrangements, and gene expression changes. Similarly, SINEs and Alu elements can play a key role in the molecular mechanisms of some hereditary diseases by making significant contributions to homologous recombination and genetic rearrangement. Consequently, TEs should not only be viewed as structural components of the genome; they should also be considered as dynamic, interactive, and evolutionarily critical elements shaping genome evolution and organism diversity. The abundance, diversity, and mobility of TEs in the genome have become a focal point of research in terms of genetic diseases, adaptive evolution, and genomic innovation.

History of Transposable Elements

Scientific studies on the existence and function of transpositional elements (TEs) are considered one of the cornerstones of modern genetics and genomics (Figure 1) (Rebollo et al. 2012). The first discovery of mobile genetic elements in eukaryotic genomes was made in the 1940s by cytogeneticist Barbara McClintock, who was working on maize (*Zea mays*). McClintock studied phenotypic changes that appeared at specific times or were reversible, and particularly linked differences in seed coloration to chromosomal rearrangements and the displacement of gene regions within the genome. These studies led to the concept of the existence of controlling elements that could move throughout the genome and influence the expression of surrounding genes. McClintock named one of these elements Dissociation (Ds) and showed that the effects of Ds were manifested in the presence of a second element called Activator (Ac). The Ac element has been identified as a transposable element that triggers the movement of Ds (McClintock, 1950).

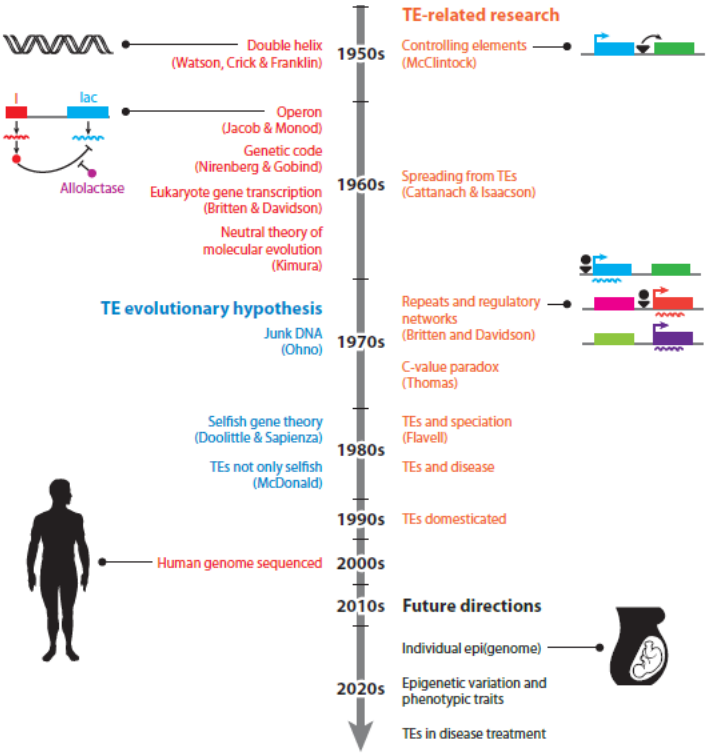

Figure 1. Timeline of Transposable Element Research: This figure summarizes major milestones in transposable element research from early molecular discoveries to modern genomic studies. It highlights key evolutionary hypotheses and emerging applications of TEs in epigenetics and disease.

In the 1970s, genetic crosses performed on *Drosophila melanogaster* revealed male recombination, infertility, and increased mutation rates that were not observed under normal conditions. These phenomena were explained by the concept of hybrid dysgenesis. During the same period, mobile DNA sequences, particularly insertion sequences (IS), were identified in bacteria and characterized at the molecular level in the Escherichia coli genome. Similarly, it was understood that elements such as the P element and the I factor, which lead to hybrid dysgenesis in Drosophila, are also mobile DNA sequences. These findings revealed that numerous transposons are present in eukaryotic and prokaryotic genomes and that some elements replicate via RNA intermediate molecules (Hua-Van & Capy, 2024).

Molecular and genetic analyses conducted in subsequent years have shown that TEs possess different structural classes and may be responsible for a significant portion of mutations, particularly those induced by physical mutagens. Phenotypic effects caused by TEs in somatic cells have been confirmed by observations such as color changes, reversible phenotypes, and slight variations. This data reveals that TEs influence gene expression and phenotype not only in the germline but also in somatic cells.

Today, thanks to genomic analyses, it is known that TEs are widespread in all living organisms, from unicellular organisms to multicellular eukaryotes. TEs constitute approximately 50% of human and other mammalian genomes and are divided into different subclasses such as LINEs, SINEs, DNA transposons, and retrotransposons. The genomic abundance and diversity of these elements demonstrate that the genome is not a static structure; rather, it exhibits a dynamic, reconfigurable organization open to evolutionary innovation. The discovery and historical study of TEs have been a critical turning point in understanding genomic organization, mutation mechanisms, and genetic diseases.

Classification of Transposable Elements

Transposable elements (TEs) are mobile DNA sequences that exhibit a wide variety in genomes and have different mechanisms of movement. Systematic classification of these elements has been a fundamental step in understanding the structural and functional properties of TEs. The first comprehensive and systematic classification of TEs was performed by Finnegan (1989). This early classification considered three main groups of TEs that could be identified at that time: (i) retroelements containing long terminal repeats (LTRs), (ii) retroelements without LTRs (non-LTR; LINEs), and (iii) DNA transposons. Finnegan's approach was based on the structure of the intermediates formed by the elements during transposition. Accordingly,

retroelements that replicate via RNA were defined as Class I, while elements that transpose directly from DNA to DNA were defined as Class II. This classification has been instrumental in understanding the fundamental mobility mechanisms of TEs (Figure 2).

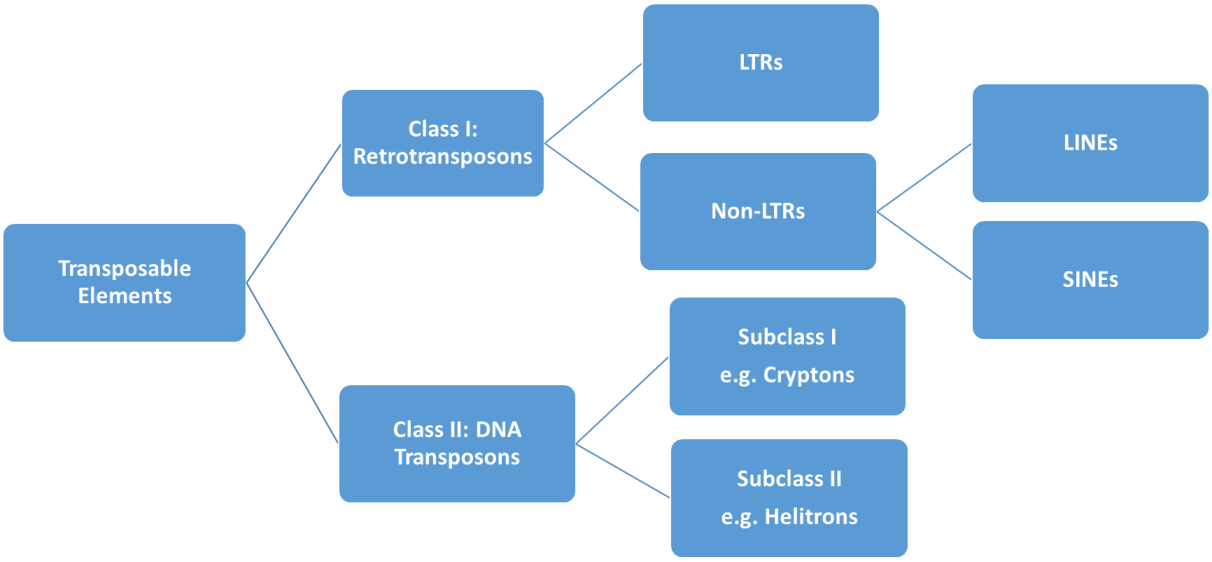

Figure 2. Classification of Transposable Elements: This diagram illustrates the hierarchical classification of transposable elements based on their transposition mechanisms. Class I elements transpose via an RNA intermediate and are divided into LTR and non-LTR retrotransposons, including LINEs and SINEs. Class II elements move through a DNA-based mechanism and include subclasses such as Cryptons and Helitrons.

For many years, TEs were evaluated and classified mostly by belonging to one of these three main groups. However, with the widespread use of genomic technologies, especially high-throughput sequencing and genome mining techniques, it has become clear that the diversity of TEs is too vast to be explained by classical systems. Extensive analyses of eukaryotic genomes have revealed previously unidentified, low-activity, or evolutionarily ancient elements; this has necessitated a reassessment of TE classification. In particular, the fact that the transposition mechanisms of some elements are still not fully understood highlights the limitations of classical classification schemes.

In this context, Curcio and Derbyshire (2003) addressed TEs with an alternative classification based on the types of enzymes involved in the integration process. This approach emphasizes that similar catalytic motifs can arise independently in different TE groups and that similar enzymatic activities are repeated in different elements evolutionarily. While this system offered a significant innovation by encompassing both prokaryotic and eukaryotic elements, it provided

a limited framework focused more on integration mechanisms due to its failure to include the full diversity of transposition processes.

A more comprehensive and up-to-date classification approach was developed by Wicker et al. (2007). This system retained Finnegan's two main class approaches but defined hierarchical subclasses, orders, and superfamilies by considering transposition mechanisms, structural features, and phylogenetic/sequence homology together. This allowed for the inclusion of numerous newly discovered TE groups in the classification and a more systematic explanation of the genomic diversity of TEs. However, Wicker et al.'s classification focused primarily on eukaryotic TEs and excluded some mobile genetic elements, such as group II introns and some bacterial elements.

These shortcomings have been partially addressed by the work of Arkhipova (2017). Arkhipova proposed a broader framework integrating previous classification systems to include both prokaryotic and eukaryotic elements, as well as other mobile genetic elements. This approach allows for a more comprehensive examination of the evolutionary origins of TEs, their mobility mechanisms, and their effects on genomes. Today, such expanded classification systems are used as standard references in both fundamental genomic research and studies investigating the association of TEs with disease and genetic variation.

Consequently, the classification of TEs is not only about categorizing sequences in the genome but also provides a critical basis for understanding mobility mechanisms, evolutionary history, and genomic effects. The development of classification has enabled a better understanding of the biological roles and pathological effects of TEs and has become a vital component of modern genomics.

Class I: Retrotransposons

Class I transposable elements (TEs), also called retrotransposons, represent the most common class of TEs in eukaryotic genomes due to their ability to form RNA intermediates during the transposition process, and the subsequent conversion of this RNA into a new DNA copy via reverse transcription. Because of these characteristics, Class I elements are particularly important in terms of their potential for spreading throughout the genome and play a critical role in increasing the genetic diversity of organisms evolutionarily.

The mechanism of action of retrotransposons is classically described as "copy-and-paste." In this mechanism, the original copy at the donor locus is preserved, and the newly synthesized

copy resulting from the transposition process is integrated into a different location in the genome. This process enables the rapid amplification of Class I elements in the genome and the accumulation of numerous copies of the same genetic material. In particular, LINE (Long Interspersed Nuclear Element) and LTR (Long Terminal Repeat) retrotransposons are the best-characterized members of this class and exert significant effects on the genome, both structurally and functionally.

Wicker et al. (2007) further subdivided Class I elements into more detailed subgroups based on structure and transposition mechanism. In this classification, LINE and LTR elements correspond to the classic A and B groups defined by Finnegan; however, less well-known and structurally atypical SINEs (Short Interspersed Nuclear Elements), DIRS, Penelope, and other retrotransposon groups are also considered within Class I. These subgroups vary in their distribution within the genome, transposition mechanisms, and evolutionary origins. For example, LINE elements are autonomous elements capable of encoding their own reverse transcriptases, while SINEs are defined as non-autonomous short sequences that replicate using the enzymatic machinery of other elements.

Class I retrotransposons not only exert structural effects on the genome but can also influence numerous molecular processes such as gene expression, chromatin arrangement, RNA processing, and genome stability. In some cases, the insertion of these elements can disrupt the coding sequences of genes or lead to alternative exon usage, contributing to phenotypic diversity. Furthermore, the accumulation of retrotransposons can pave the way for expansion of genome size and the emergence of novel genetic combinations over an evolutionary timescale.

Consequently, Class I elements play a central role in the evolution and dynamics of eukaryotic genomes, both in terms of their genomic diffusion potential and molecular effects. The autonomy of LINE and LTR elements, their interactions with dependent elements such as SINE, and their ability to replicate via RNA are key features that enhance the genetic diversity and evolutionary innovation capacity of Class I retrotransposons (Wicker et al., 2007).

LTR Retroelements

LTR (Long Terminal Repeat) retroelements are a group of Class I transposable elements that are largely similar to retroviruses in terms of their structural and functional characteristics. These elements typically have a DNA sequence a few kilobases long with long terminal repeat (LTR) sequences at both ends. LTRs have critical functions in regulating both transposition and

element expression; they contain promoter, enhancer, and polyadenylation signals. The open reading frames (ORFs) encoded by LTR retroelements are responsible for the production of the structural and enzymatic proteins necessary for the transposition process.

The first ORF typically encodes structural proteins involved in the formation of virus-like particles (VLPs), while the second ORF enables the synthesis of a polyprotein containing enzymes such as reverse transcriptase (RT), RNase H, and integrase (Malicki et al., 2020). The transposition process begins with the production of the element's RNA transcript; this RNA is then packaged into VLPs with the help of necessary proteins. Reverse transcription converts the RNA into DNA, and this new DNA copy is integrated into a new locus in the genome via the integrase enzyme. This mechanism allows LTR retroelements to replicate via a copy-and-paste strategy, resulting in the formation of many repetitive sequences in the genome.

LTR retroelements are divided into different superfamilies based on phylogenetic and structural characteristics. Among these superfamilies, Copia, Gypsy/Ty3, BEL/Pao, and Endogenous Retroviruses (ERVs) stand out. For example, ERVs represent sequences of retroviral origin in the human genome and show close phylogenetic relationships with infectious retroviruses in the Retroviridae family. The fundamental difference between LTR retroviruses and LTR retrotransposons is that retroviruses have the capacity to cause intercellular infection, whereas LTR retrotransposons complete their life cycle entirely within the intracellular environment (Malicki et al., 2020).

However, some LTR retroelements may theoretically carry additional envelope (env) genes with the potential for intercellular transmission. The Gypsy element in *Drosophila melanogaster* is a classic example of this. Although initially identified as a retrotransposon, Gypsy has gained the ability to intercellularly transmit thanks to its envelope gene and is functionally considered a virus. This demonstrates that LTR retroelements independently gain and lose the envelope gene in different lineages evolutionarily, leading to diversity in their intragenomic transmission capabilities.

A subgroup of LTR retroelements, DIRS (Dictyostelium Intermediate Repeat Sequences) elements, are distinctly different from classic LTR retroelements. Although these elements also possess LTR sequences, LTRs can be found either directly or in reversed form depending on the family, and contain internal terminal sequences critical for transposition. DIRS elements encode a reverse transcriptase that is phylogenetically related to LTR retroelements, but perform a unique integration mechanism using tyrosine-dependent recombinase instead of DDE

motif integrase. Because of these characteristics, DIRS elements represent a relatively poorly defined and rare group among Class I retrotransposons. Studies to date have revealed that DIRS elements are classified into at least four different superfamilies and are molecularly distinct from other LTR retroelements (Malicki et al., 2020).

LTR retroelements play a critical role in genomic evolution and diversity. Processes such as intragenomic rearrangements, exon skipping, regulation of gene expression, and modification of chromatin structure are directly related to the presence of these elements. Furthermore, new DNA copies formed via LTR retroelements contribute to both increased genome size and the evolutionary emergence of new genetic combinations. For these reasons, LTR retroelements are considered a dynamic and mobile part of eukaryotic genomes.

Non-LTR Retrotransposons

Non-LTR (Long Terminal Repeat-less) retrotransposons are important Class I transposable elements that, despite lacking LTR sequences, possess structural motifs and sequences critical to the transposition process. The 3′ ends of these elements typically contain TA-rich sequences or short repeat sequences containing polypyrimidine/polypurine; these structures provide essential functional requirements for reverse transcription and genomic integration (Arkhipova, 2017).

The best-known and largest representatives of non-LTR retrotransposons are LINEs (Long Interspersed Nuclear Elements). LINEs typically contain two open reading frames (ORFs): ORF1 encodes an RNA-binding and GAG-like protein, while ORF2 contains both reverse transcriptase (RT) and often an endonuclease domain. These structural features allow LINEs to integrate their own RNA transcripts into DNA, thus integrating them into a new genomic locus. Transposition of LINEs occurs via a unique mechanism called target-primed reverse transcription (TPRT). In this process, premature termination of reverse transcription at the 5′ end of the RNA template is common; this results in the accumulation of numerous “dead” copies in genomes with shortened 5′ ends and inability to transpose (Kojima, 2020; Arkhipova, 2017).

LINEs are divided into five main superfamilies based on endonuclease and RT phylogeny: L1, L2, RTE, CR1, and Tx1. This classification provides an important reference for studying the evolutionary origins and structural relationships of the elements (Arkhipova, 2017; Kojima, 2020).

Another group closely related to LINEs in terms of function are Short Interspersed Nuclear Elements (SINEs). SINEs lack coding capacity and are therefore dependent on the enzymatic machinery provided by LINEs for transposition. Generally derived from small RNA molecules such as tRNA, 7SL RNA, or 5S rRNA, SINEs can reach very high copy numbers in some genomes. In the human genome, Alu elements constitute the best-known example of SINEs and are estimated to comprise approximately 10% of the genome (Arkhipova, 2017; Kojima, 2020).

Non-LTR retrotransposons also include Penelope-like elements (PLEs). Unlike classical LINEs and SINEs, these elements contain a phylogenetically close RT to eukaryotic telomerase reverse transcriptase (TERT) and carry atypical repeat sequences called pseudo-LTRs. The widespread presence of PLEs in genomes has demonstrated their existence in all major eukaryotic kingdoms, and it is suggested that these elements may undertake potential functions in maintaining genome stability and telomere structure (Craig et al., 2021).

Non-LTR retrotransposons play a central role in genomic evolution and diversity. The integration of LINEs and SINEs can contribute to chromosomal rearrangements, modulation of gene expression, and the formation of novel gene structures. The genomic distribution and high copy number of these elements reveal their evolutionary potential to provide both adaptation and genetic diversity.

Class II: DNA Transposons

Class II transposable elements (TEs) are important genomic elements that move through DNA and mostly utilize a “cut-and-paste” mechanism. These elements are defined via terminal inverted repeats (TIRs) in the genome, and transposases with DDE motifs play a key catalytic role in transposition processes. TIR transposons constitute the most common Class II representatives in eukaryotic genomes, and approximately 20 superfamilies have been identified to date; these elements are known to be present in almost all sequenced genomes (Yuan and Wessler, 2011; Kojima, 2020).

During transposition, double-stranded DNA breaks (DSBs) occur at the donor locus. These breaks can potentially be damaging to the genome; however, cellular repair mechanisms such as homologous recombination (HR) or non-homologous end joining (NHEJ) can repair this damage and, in some cases, contribute to the replication of the elements. This situation demonstrates that Class II TEs can have bidirectional effects on both genomic diversity and genetic stability (Feschotte and Pritham, 2007).

Class II contains several subgroups:

Cryptons: These elements are unique DNA transposons that utilize tyrosine recombinase and lack classical TIR sequences at their ends. It has been suggested that cryptons may have an evolutionary relationship with DIRS retroelements and that some domesticated forms may play a functional role in the human genome (Goodwin et al., 2003; Kojima and Jurka, 2011).

Helitrons: Helitrons behave via a rolling-circle replication-like mechanism and are characterized by Rep/helicase domains. These elements have been shown to replicate in the genome via a unique transposition mechanism called "peel-and-paste" (Kapitonov and Jurka, 2001; Grabundzija et al., 2018; Kosek et al., 2021). Helitrons play important roles in the evolution of the host genome, generally mediating gene transfer and recombination processes.

Polytrons (Mavericks): Polytrons are large and complex DNA transposons carrying both the DDE transposase and DNA polymerase B genes. These elements stand out in terms of genome size and constitute a significant portion of the genome in some species. Although the transposition mechanisms of polytrons are not yet fully elucidated, they are known to have the potential for both autonomous replication and the creation of genetic diversity (Kapitonov and Jurka, 2006; Pritham et al., 2007).

Non-autonomous short derivatives: Many TE groups contain short elements that have lost their own coding capacity. These elements act using the enzymatic machinery provided by autonomous TEs. Examples of this group include TIR-derived MITEs (Miniature Inverted-repeat Transposable Elements), LINE and LTR-derived short elements, and retrozymes identified in plants (Cervera and de la Peña, 2020).

The genomic effects of Class II TEs are not limited to transposition; these elements also play a role in processes such as gene expression modulation, gene rearrangements, chromosomal breaks, and the formation of new genetic combinations. Furthermore, the interaction between autonomous and non-autonomous elements is a significant determinant in shaping genome architecture.

In conclusion, the structural and mechanistic diversity of Class II TEs is not only a matter of classification but also provides a fundamental framework for understanding genome evolution and the formation of regulatory networks. Mechanistic differences between retrotransposons and DNA transposons determine copy number dynamics, target integration patterns, and the degree of autonomy of elements within the genome. Modern classification approaches allow us

to interpret the evolutionary impacts, regulatory functions, and contributions to genetic diversity of these elements in a more holistic way.

2. Evolution and Transposable Elements

For a long time, genomes were viewed as passively stored structures where genetic information was passed down largely unchanged across generations. This approach considered DNA simply a static template of protein-coding genes and fixed structural regions. However, recent research has revealed that genomes are far more than this simple definition. Genomes are now understood not merely as information repositories governing the functions of an organism, but as complex ecosystems containing dynamic elements that can move, reproduce, and determine their own evolutionary destiny.

Transposable elements (TEs) are one of the most striking examples of these dynamic elements. In a sense, they can be described as the invisible but effective “demons” of the genome; some are tightly suppressed by the host genome, while others can multiply uncontrollably, reshaping the genomic architecture. TEs demonstrate that they are not only structural components of the genome but also active players in evolutionary processes. They play a critical role in the creation of genetic diversity and adaptation processes. They allow species to respond to environmental changes through new mutations and rearrangements.

The evolutionary impact of TEs is not limited to creating genetic variation. Their translocation within the genome affects the regulation of genes and regulatory regions, leading to the formation of new gene networks and changes in gene expression patterns. In some cases, TEs can mediate the emergence of new genes or gene combinations; in other cases, they can pave the way for genetic disruptions and diseases. This dual effect positions TEs as both a source of evolutionary innovation and a harbinger of potential dangers.

In addition, the diversity and prevalence of TEs within the genome offer important clues to understanding interspecies evolutionary relationships. TE types and activities in different organisms carry traces of evolutionary history, providing information about speciation processes and adaptive strategies. In this respect, TEs should be considered not only as "parasites" of the genome but also as fundamental elements of evolutionary innovation and genomic plasticity.

In conclusion, transposable elements demonstrate that genomes are not static repositories of information, but rather dynamic structures that are constantly in motion, responding to

evolutionary pressures and shaping the biological fate of the host organism. This role of transposable elements makes them indispensable research objects for understanding evolutionary biology, genomic innovation, and speciation processes.

Evolutionary Reasons for Changes in Transposable Element Activity

In eukaryotic genomes, transposable elements (TEs) exhibit almost universally persistent activity despite the multilayered and sophisticated silencing mechanisms developed by the host. While it is known that sequences derived from TEs can sometimes provide adaptive or regulatory advantages to the host organism, TE activity is generally parasitic in nature and potentially detrimental to genome integrity. This makes it logical that defense mechanisms suppressing TE activity at the host level are evolutionarily supported.

However, the fact that TEs cannot be completely eliminated is considered a significant paradox from an evolutionary biology perspective. The role of the strong pleiotropic effects of TE silencing systems is primarily highlighted in explaining this paradox. Small RNA-based silencing pathways, beyond controlling TE mobility, play critical roles in fundamental biological processes such as germline development and the maintenance of genome integrity. Therefore, further strengthening these silencing mechanisms can create undesirable negative effects on processes vital to the host.

Furthermore, off-target effects of host-mediated TE silencing must also be considered. The spread of epigenetic repressive marks from TE sequences to neighboring genomic regions can lead to the accidental silencing of genes and thus harmful phenotypic consequences for the organism. Since most TE silencing systems have evolved to target broad groups of TEs, the development of more specialized defense strategies that would completely eliminate specific TE families may be limited.

The second important reason explaining the maintenance of TE activity rests on a more general question in evolutionary biology: why can't mutations be completely eliminated? Both mutations and TE transposition constitute fundamental sources of genetic variation critical to adaptive evolution. The inability to completely halt these processes may not be directly explained by adaptive benefits; instead, it is related to the limitations of natural selection and the dynamics of population genetics. In particular, the selective advantage gained from further reducing low TE and mutation rates is limited.

For an allele to be maintained by selection against random loss, the benefit it provides must be strong enough to be inversely proportional to the effective population size. Otherwise, regulatory variants that reduce TE activity, even if beneficial, cannot be fixed in the population. Therefore, maintaining a low but sustained level of activity, rather than the complete elimination of TEs, is an evolutionarily expected outcome.

Finally, the persistence of TE activity is a natural consequence of the direct evolutionary conflict of interest between the host genome and TEs. Host-level selection suppresses the mobility of TEs to maintain genome integrity, while selective pressure on TE sequences aims to increase their own replication and dispersal capabilities. These opposing selective forces lead to a continuous evolutionary arms race between the host and TEs, ensuring that TEs maintain low but sustained activity within the genome.

Evolutionary Consequences of Changes in Transposable Element Activity

The activity of transposable elements (TEs) can have largely detrimental effects on genome integrity; these effects include mutations, chromosomal rearrangements, and in some cases, the emergence of genetic diseases. However, considering evolutionary timescales, it would be incomplete to say that TE activity only produces negative consequences. On the contrary, rare but impactful TE insertions have played a critical role in the emergence of phenotypic innovations that enhance the adaptive potential of host organisms.

The best-documented examples of the evolutionary effects of TEs are the acquisition of advantageous phenotypes through insertions or rearrangements occurring in gene regulatory regions. In this context, the spotted moth (Biston betularia) can be cited as a classic and iconic model. During the Industrial Revolution in England, the interaction between increased coal pollution and bird predation led to the replacement of the previously dominant light-colored typica form with the dark-colored carbonaria form. This change is a clear example of evolutionary adaptation that arose in response to natural selection and directly reflects environmental adaptation (Cook, 2003).

Analyses at the molecular level revealed that the mutation underlying this phenotypic transformation was a TE containing large, consecutive repeats inserted into the first intron of the cortex gene. Using the geographical distribution and statistical data of reassembled carbonaria haplotypes, Hof et al. showed that this transposition event occurred around 1819, a date consistent with historical records (Hof et al., 2016).

These findings demonstrate that TE insertions can play a direct role in microevolutionary changes and clearly position TEs as a significant source of phenotypic innovation in the genome. This particular example highlights that TE activity is not only detrimental to the genome but also a critical creative force in adaptive evolution.

Transposable Elements and Chromosome-Scale Evolutionary Adaptation

The evolutionary effects of transposable elements (TEs) are not limited to single gene mutations. Unlike typical point mutations, TEs have the capacity to replicate themselves within the genome; each new insertion potentially creates a new source of transposition, providing an exponential replication mechanism. This replicative feature leads to the formation of repeat sequences distributed throughout the genome, and these sequences pave the way for rapid structural and regulatory changes at the chromosome or genome scale.

The potential of TEs to spread the same regulatory motifs to different regions of the genome makes coordinated evolutionary changes possible. This idea was first proposed by Britten and Davidson (1971) and has since been widely discussed (Chuong et al., 2017; Feschotte, 2008; Fueyo et al., 2022). Thus, the indirect effects of TE activity can contribute to adaptive changes not on individual genes, but on entire chromosomes or large genomic regions.

An example of chromosome-wide evolutionary transformations is the rapid dose compensation evolution observed in *Drosophila miranda*. This mechanism, achieved through hypertranscription of the X chromosome in males, relies on the presence of recognition motifs distributed along the X chromosome. In D. miranda, the transformation of an initially autosomal chromosome into a new X chromosome led to the emergence of an efficient dose compensation system in a short evolutionary time span (Zhou et al., 2013).

In this process, rather than the formation of the necessary recognition motifs through independent mutations, the repeated insertion of ISX, a Class II TE containing motif-like sequences, onto the new X chromosome established an efficient chromosome-wide dose compensation mechanism (Ellison and Bachtrog, 2013). Similarly, instances where rapidly amplified TEs contribute to the evolution of dosage compensation have recently been observed in fish (Metzger et al., 2023).

A similar scenario may have played a role in the evolution of X chromosome inactivation in placental mammals. Unlike the mechanism in flies, dosage compensation in mammals is achieved through the random silencing of one of the two X chromosomes in females. This

chromosome-specific silencing is supported by significantly enriched LINE-1 splices on the X chromosome (Bailey et al., 2000). X chromosome regions with few LINE-1 splices are rich in genes that escape X inactivation; this suggests that LINE-1 sequences play a facilitating role in silencing (Chow et al., 2010).

Furthermore, LINE-1 enrichment on the X chromosome has been shown to extend back to the evolutionary origins of placental mammals (Escamilla-Del-Arenal et al., 2011). On the other hand, the absence of a similar LINE-1 accumulation on the X chromosomes of marsupials suggests that the increase in LINE-1 activity and the associated chromosome-wide spread of cis-regulatory elements may have facilitated the transition to random X inactivation in eutherians (Bailey et al., 2000).

Transposable Elements and Their Contribution to Interspecies Reproductive Isolation

Changes in the activity of transposable elements (TEs) not only affect intraspecies adaptive processes but can also play a significant role in the evolution of interspecies reproductive isolation. Reproductive isolation functions as a fundamental mechanism in the formation of new species and is shaped by the accumulation of genetic incompatibilities that limit gene flow. In this context, TEs are considered dynamic elements that contribute to the acceleration of isolation processes due to their high genomic exchange capacity.

The contribution of TEs to reproductive isolation is particularly evident through intergenomic incompatibilities. Differences in TE content, copy number, and repression mechanisms between different populations or species can lead to disruption of genomic balance in hybrid individuals. This facilitates the emergence of postzygotic isolation mechanisms such as developmental anomalies, infertility, or reduced viability (Widen et al., 2023).

Changes in the activity of transposable elements (TEs) not only affect intraspecies adaptive processes but can also play a significant role in the evolution of interspecies reproductive isolation. A classic example of this phenomenon is the hybrid dysgenesis observed in Drosophila species. As previously mentioned, sterility, increased mutation rates, and chromosomal abnormalities have been observed in certain crosses between natural populations and laboratory lines. The source of these effects is the differences in the TE repertoires in the parental lines. Transposons, particularly the P element and I factor, are activated uncontrollably in embryos lacking repression mechanisms, leading to significant genomic damage in the germline (Parhad et al., 2017). This example clearly demonstrates that TEs can directly contribute to the formation of interspecies genetic incompatibilities.

Similar mechanisms have been reported in plants and other animal groups. In plants, increased TE activity after hybridization leads to a condition called "genome shock," causing a rearrangement of gene expression patterns. This process contributes to the preservation of species boundaries by preventing some hybrid individuals from surviving (Hénault, 2021).

The contribution of transposable elements (TEs) to reproductive isolation is not limited to harmful effects. In some cases, TE-induced regulatory changes can lead to rapidly diverging gene expression profiles among populations. These divergences, especially when affecting behavioral, physiological, or reproductive-related traits, can also indirectly support the evolution of prezygotic isolation mechanisms.

Consequently, transposable elements are considered not passive byproducts of genomic diversity, but dynamic elements that play an active role in speciation processes. Differences in TE activity facilitate the formation of both postzygotic and prezygotic reproductive isolation mechanisms and can determine the speed and direction of evolutionary divergence.

Transposable Elements and Evolutionary Equilibrium

The data examined indicate that the presence of transposable elements (TEs) within genomes is not a random feature, but rather the result of a dynamic equilibrium shaped throughout evolutionary processes. The fact that TEs are largely silenced but not completely eliminated in eukaryotic organisms points to an ongoing evolutionary struggle between the host genome and TEs, shaped by mutual selection pressures.

When examining the evolutionary causes of TE activity, prominent factors include the pleiotropic effects of silencing mechanisms developed by the host, the limits of natural selection effectiveness, and selection pressures that support the self-replication of TE sequences (Charlesworth and Langley, 1989; Le Rouzic and Capy, 2005; Lynch and Conery, 2003; Chuong et al., 2017). These factors are considered key elements explaining the persistence of TE activity, even at low levels, over long evolutionary timescales.

In addition, the evolutionary consequences of TE activity are not limited to genomic instability and deleterious mutations. Some TE insertions can lead to changes in gene regulation, contributing to the emergence of phenotypic diversity that supports adaptation to environmental conditions (Feschotte, 2008; Chuong et al., 2017). Furthermore, the capacity of TEs to replicate and spread throughout the genome plays a critical role in the evolution of regulatory mechanisms at the chromosome level. In particular, complex regulatory processes such as

dosage compensation can evolve effectively over short evolutionary timescales thanks to the distributed motifs provided by TE insertions (Ellison and Bachtrog, 2013; Metzger et al., 2023).

Finally, the differing TE contents between species and the molecular mechanisms involved in silencing these elements can lead to genomic incompatibilities in hybrid individuals, thus accelerating the formation of interspecies reproductive isolation. In this respect, TEs are among the fundamental components not only of adaptive evolution but also of speciation processes.

3. From Silent Genome to Active Mobile Elements: Factors Initiating TE Activation

Transposable elements (TEs) are tightly repressed to maintain cellular genome integrity, primarily through DNA methylation, histone modifications, and RNA-mediated silencing mechanisms. However, this regulatory network can become vulnerable to environmental and endogenous stressors to which the cell is exposed. Factors such as ionizing and non-ionizing radiation, environmental pollutants, chemical toxins, and nutrition-related epigenetic changes have been shown to alter the methylation status and transcriptional activity of TEs. Such exposures can lead to increased TE expression and, in some cases, active retrotransposition as a result of weakening epigenetic repression. This section discusses the main environmental factors and underlying molecular mechanisms shown to trigger TE activity, within the framework of current literature.

Effects of Radiation on Transposable Element Activity

Both ionizing and non-ionizing radiation types can profoundly affect epigenetic regulatory mechanisms, in addition to their direct damaging effects on genome integrity. Recent evidence reveals that radiation exposure not only leads to genetic mutations but also reshapes the repression status of transposable elements (TEs) through DNA methylation, histone modifications, and changes in chromatin structure. In this context, radiation is considered an indirect but effective environmental stressor in triggering TE activity. Epigenetic reprogramming, which occurs depending on the type, dose, and duration of radiation exposure, can lead to changes in the methylation levels of TEs and accompanying increases in their expression. Comparative examination of the effects of different physical stressors, such as terrestrial radiation, space radiation, and ultraviolet rays, on TEs is important for understanding the long-term consequences of environmental factors on genomic stability. This section will discuss experimental and epidemiological findings regarding the effects of different types of radiation on TE methylation, expression, and retrotransposition activity.

Effects of Terrestrial Radiation on Methylation and Expression of TEs

Terrestrial radiation consists mainly of photons with low linear energy transfer (LET), such as X and γ rays, and is characterized by relatively diffuse energy accumulation in cells. This type of radiation can produce genotoxic effects such as DNA single and double-strand breaks, oxidative damage, and mutation induction. However, it is increasingly understood that ionizing radiation targets not only DNA integrity but also epigenetic regulation. In previous studies, hypermethylation patterns of tumor suppressor genes have been identified in lung cancers of individuals occupationally exposed to ionizing radiation (Lyon et al., 2007). In addition to gene-specific epigenetic changes, numerous data from in vivo studies demonstrate that radiation exposure is associated with a loss in global DNA methylation (Loree et al., 2006; Giotopoulos et al., 2006; Koturbash et al., 2008; Wang et al., 2014). In a study by Miousse et al., significant epigenetic changes were observed in mouse bone marrow mononuclear cells and hematopoietic stem/progenitor cells exposed to 56Fe ions (600 MeV; 0.1, 0.2, and 0.4 Gy). Four weeks after radiation, dose-dependent hypermethylation of the repeating elements LINE-1 and SINE B1 was reported, particularly in hematopoietic stem/progenitor cells [4.2-fold increase for LINE-1 ($P < 0.001$); 7.6-fold increase for SINE B1 ($P < 0.01$); [$n = 5$]. However, it has been reported that the epigenetic profile reversed at later time points; a significant decrease in global DNA methylation (1.9-fold; $P < 0.05$), a decrease in Dnmt1 expression (1.9-fold; $P < 0.01$), and an increase in LINE-1 and SINE B1 expression were observed (2.8-fold increase for LINE-1 after 0.4 Gy exposure; 1.9-fold increase for SINE B1; $n = 5$). These epigenetic changes were shown to be persistent and detectable for at least 22 weeks after exposure. Notably, exposure to 56Fe ions was not reported to be associated with increased reactive oxygen species production, significant DNA strand breaks, cellular senescence, or apoptosis. These findings suggest that the effects of ionizing radiation on TEs may arise through epigenetic reprogramming rather than direct genotoxic damage (Miousse et al., 2014).

Effects of Space Radiation on Methylation and Expression of TEs

The increasing use of proton radiation in clinical applications and the growing interest in space research have necessitated a detailed investigation of the biological effects of exposure to space radiation. Protons and heavy ions, the main components of space radiation, cause more intense and clustered DNA damage compared to terrestrial radiation, and repair of this damage is often difficult or impossible. This is associated with higher relative biological activity in cell death (Blakely and Kronenberg, 1998).

In a study conducted in cell culture models, Goetz et al. showed that the epigenetic effects of space radiation differ from the patterns created by terrestrial radiation. Human diploid skin fibroblasts and human colorectal cell lines were exposed to low mean absorbed doses of protons (150 MeV/n; LET 0.55 keV/μm) or 56Fe ions (1 GeV/n; LET 150 keV/μm), and significant hypomethylation was detected in the L1 and Alu elements after 16–20 passages following radiation induction (Goetz et al., 2011). Similar results were obtained in a study by Aypar et al. on the human-hamster hybrid cell line GM10115. In this study, it was shown that exposure to 1 Gy of 56Fe ions led to hypomethylation in both L1 and Alu elements, while a lower dose of 0.1 Gy did not significantly affect the methylation status of these retrotransposons (Aypar et al., 2011).

Exposure to Ionizing Radiation and L1 Retrotransposition

In a study conducted by Tanaka et al., retrotransposition activity was evaluated in the human glioma cell line NP2, which carries the L1 reporter system, using both X-rays (0–10 Gy) and carbon ion beams (0–4 Gy). Both types of radiation were shown to significantly increase the frequency of L1 transcription. The study also revealed that X-rays predominantly induced 5′-end truncated L1 splices, whereas carbon ion beams promoted full-length or long-dimensional L1 splices (Tanaka et al., 2012). These findings demonstrate that ionizing radiation can affect not only TE expression but also the structural properties of the resulting retrotransposition products.

Effects of UV Radiation on TEs

It is known that solar ultraviolet (UV) radiation affects numerous biological processes in human skin, such as inflammation, immunosuppression, cell death, and premature aging. UV radiation can also play a role as both a tumor initiator and tumor promoter in skin carcinogenesis (Ichihashi et al., 2003). In a study by Nair-Shalliker et al., the outdoor UV exposure of 208 individuals living in South Australia over the last six weeks was evaluated, and LINE-1 methylation levels in peripheral blood lymphocytes were analyzed using the pyrosequencing method. A significant relationship was found between increased solar UV exposure and decreased LINE-1 methylation; it was suggested that this could support LINE-1 reactivation through UV exposure-induced hypomethylation (Nair-Shalliker et al., 2014).

Effects of Chemical Exposures on Transposable Element Activity

Chemical environmental exposures are among the most common and diverse stressors affecting genome integrity. Numerous chemical agents, such as industrial pollutants, air pollution components, heavy metals, and organic toxins, can directly cause DNA damage, as well as affect genome function in a more indirect but permanent way by targeting epigenetic regulatory mechanisms. These effects have critical consequences, particularly for DNA methylation and chromatin-based defense systems involved in the repression of transposable elements (TEs). Accumulated experimental and epidemiological data show that chemical exposures can lead to disruptions in the methylation status of TEs, and these changes are often characterized by hypomethylation in repetitive elements such as LINE-1 and Alu. Weakening of TE repression can pave the way for transcriptional reactivation of these elements and increased genomic instability. This suggests that the triggering effect of chemicals on TE activity may be a mechanism operating independently of, but in interaction with, mutational damage. In particular, common exposure sources such as air pollution, diesel exhaust, volatile organic compounds, and heavy metals are proposed to influence TE regulation through cellular methyl donor balance, DNA methyltransferase activity, and oxidative stress responses. This section will address the effects of different chemical agents on TE methylation and expression, in light of epidemiological findings from human populations and experimental studies in cell and animal models.

The Effects of Air Pollution and Particulate Matter (PM) on TE Methylation

Ambient air pollution, particularly fine and coarse particulate matter (PM), is a complex source of environmental exposure that can have multifaceted effects on human health. Recent epidemiological and experimental studies have revealed that exposure to air pollution affects genome function not only through inflammation and oxidative stress but also through epigenetic mechanisms. In this context, the methylation status of transposable elements (TEs) stands out as an epigenetic indicator sensitive to environmental air pollutants.

In the study conducted by Peluso et al., individuals living in the Ma Ta Phut industrial area in Thailand were compared with industrial workers employed in this area and a control group living in a rural area. Within the scope of the study, long-range nuclear element-1 (LINE-1) methylation levels and DNA damage indicators were evaluated. The findings showed that occupational exposure in individuals working in large-scale steel, oil refinery, and petrochemical plants in industrial areas was associated with lower LINE-1 methylation in

peripheral blood leukocytes (Peluso et al., 2012). Specifically, LINE-1 methylation levels observed in industrial area workers were reported to be significantly lower compared to individuals living in the same area but without industrial exposure (74.8% vs. 78%; $p<0.001$). These results suggest that chronic exposure to air pollutants may be associated with weakening of TE suppression.

The effects of air pollution on TEs are also supported in experimental models. In a study conducted by Miousse et al., mouse RAW264.7 macrophage cells were exposed in vitro for a short period (24 hours) to an aqueous extract of PM10 present in ambient air. Although no significant change in global DNA methylation levels was observed in the study, a redistribution of methylation patterns in repetitive elements such as LINE-1, SINE B1, and SINE B2 was reported (Miousse et al., 2014). This suggests that the effects of chemical exposures on TEs may occur through target-specific and element-selective mechanisms rather than global epigenetic changes. In the same study, a dose-dependent decrease in the expression of DNA methyltransferases (Dnmt1, Dnmt3a, and Dnmt3b) responsible for de novo DNA methylation was detected. This finding suggests that particulate matter exposure may create an epigenetic environment that can lead to both global and TE-related hypomethylation at later time points. Furthermore, it has been reported that PM exposure causes dose-dependent reactivation of the SINE B2 element, regardless of methylation status. These results support the idea that histone modifications and non-coding RNAs may play a role in regulating TE transcription in response to chemical exposures (Miousse et al., 2014). Overall, air pollution and particulate matter exposure can create a favorable environment for the reactivation of these elements by targeting the mechanisms involved in the epigenetic repression of TEs. This suggests that the contribution of environmental chemical exposures to genomic instability and disease risk may occur, at least in part, through changes in TE activity.

Tobacco Smoke Exposure

Tobacco smoke is a significant source of environmental exposure that can affect genome integrity and epigenetic regulatory mechanisms due to its complex chemical composition. Under potentially relevant exposure conditions, experimental studies in which human bronchial epithelial cells (HBEC) and fully transformed A549 lung cancer cells were exposed to intense cigarette smoke for up to nine months reported significant DNA methylation loss in LINE-1 (L1) elements (Liu et al., 2010). This epigenetic alteration was shown to be associated with decreased function of DNMT1 DNA methyltransferase, which is responsible for maintaining

DNA methylation; the authors suggested that this decrease in DNMT1 activity could constitute a possible mechanism for L1 hypomethylation.

Traffic-Related Pollutants and the Effects of Diesel Exhaust on TE Methylation

Traffic-related air pollution, particularly diesel exhaust emissions, is a significant environmental stressor to which human populations are widely exposed. Diesel exhaust consists of a highly complex chemical mixture including 1,3-butadiene, polycyclic aromatic hydrocarbons (PAHs), formaldehyde, benzene, acetaldehyde, and diesel exhaust particulate matter. This complex composition makes it difficult to fully elucidate the mechanisms underlying the biological effects of diesel exhaust, and especially its carcinogenic potential. In a double-blind, crossover design study conducted by Jiang et al., the effects of short-term diesel exhaust exposure on circulating blood DNA methylation were investigated in 16 non-smoking asthmatic individuals. Blood samples were taken before exposure, 6 hours after exposure, and 30 hours after exposure; DNA methylation profiles were analyzed using the Illumina Infinium HumanMethylation450 array. The study results showed that the methylation changes observed in LINE-1 and Alu elements after exposure to diesel exhaust were not unidirectional, with both hypomethylation and hypermethylation regions occurring simultaneously. Specifically, an increase in DNA methylation was detected in 13 of the 31 different LINE-1 loci identified genome-wide, while a decrease was detected in 18. Similarly, hypermethylation was observed in 12 of the 25 Alu loci exhibiting different methylation profiles in response to diesel exhaust, and hypomethylation in 13. These findings reveal that the effects of short-term diesel exhaust exposure on TE methylation are heterogeneous and locus-specific (Jiang et al., 2014). Therefore, it appears that traffic-related chemical exposures can affect the epigenetic regulation of TEs in a complex and context-dependent manner.

Chemical Exposures and Transposable Element Activity

It is becoming increasingly clear that environmental chemical exposures are not limited to direct toxic effects on the genome; they can also affect transposable element (TE) activity through epigenetic regulatory mechanisms. In particular, changes in DNA methylation patterns can pave the way for the reactivation of TE families such as LINE and SINE, which are normally suppressed. In this context, evaluating the effects of exposure to different chemical agents on TE silencing is important for understanding how genomic stability is shaped by environmental factors.

The Effect of Occupational Benzene Exposure on Hypomethylation in LINE-1 and Alu Elements

In a study conducted by Bollati et al., 78 petrol station workers and 77 urban traffic officers in Italy who were occupationally exposed to low levels of benzene were compared with a reference group of 58 people in Milan who were not exposed to benzene. The study showed that benzene exposure was associated with a 2.33% decrease in LINE-1 (L1) methylation ($p = 0.009$) and a significant 1.00% hypomethylation in Alu elements ($p = 0.027$) (Bollati et al., 2007). In another study conducted by Fustinoni et al., supporting the findings of Bollati et al., it was reported that the hypomethylation observed due to occupational benzene exposure was associated with the levels of trans,trans-muconic acid, a metabolite of benzene. In this study, a negative correlation was found between t,t-muconic acid and both L1 and Alu methylation levels (Fustinoni et al., 2012).

Effect of 1,3-Butadiene Exposure on Hypomethylation and TE Reactivation in Transposable Elements

In a study by Koturbash et al., it was shown that male C57BL/6 mice exposed to 1,3-butadiene via inhalation for two weeks experienced a significant decrease in methylation levels of L1 ORF1, SINE B1, and SINE B2 elements in their liver tissues. These changes were reported to be strongly correlated with losses in global DNA methylation. Importantly, this study demonstrated that TE hypomethylation due to 1,3-butadiene exposure exhibited a dose-dependent response; higher concentrations made the methylation loss in TE sequences more pronounced. Furthermore, 1,3-butadiene-induced TE hypomethylation has been reported to be associated with reactivation of these elements in later stages (Koturbash et al., 2011).

Arsenic Exposure and Decreased LINE-1 DNA Methylation

Arsenic needs to be reduced and methylated for detoxification and removal from cells. In this process, arsenic places a significant burden on cellular methylation capacity. Studies have shown that chronic arsenic exposure leads to global DNA hypomethylation, a decrease in S-adenosylmethionine levels (the main methyl group donor for DNA methylation), and a decrease in DNA methyltransferase activity (Zhao et al., 1997; Xie et al., 1997). In a population-based case-control study conducted in New Hampshire, USA, by Wilhelm et al., blood samples from 459 adult individuals were analyzed. The study found that arsenic exposure was associated with a significant decrease in LINE-1 methylation ($p = 0.04$) (Wilhelm et al., 2010). In a case-control study focusing on bladder cancer conducted in the same population, LINE-1 methylation status

in bisulfite-modified DNA samples obtained from blood was evaluated using the pyrosequencing method; arsenic levels were shown to be associated with decreased LINE-1 methylation ($p = 0.04$).

Mercury and LINE-1 Activation

In a study conducted by Habibi et al., it was reported that mercury exposure increased the activity of LINE-1 (L1) retrotransposons in the BE(2)-M17 human neuroblastoma cell line. This study showed that mercury led to a significant increase in L1 mRNA and protein levels, resulting in an increased frequency of genomic retrotransposition (Habibi et al., 2014).

A noteworthy finding is that this effect of mercury was observed only in neuroblastoma cells; a similar increase was not detected in non-neuronal cell lines. The researchers suggested that mercury, a neurotoxic agent, can have long-term effects on DNA, particularly in neuronal cells, by increasing L1 activity, even at non-toxic concentrations, thus making these cells more susceptible to neurodegenerative processes over time.

The Regulatory Role of Nutrition on Transposable Element Activity

Nutrition stands out as a critical environmental factor in shaping genomic regulation through epigenetic mechanisms. In particular, the sensitivity of epigenetic markers such as DNA methylation and histone modifications to dietary components can have a decisive effect on the repression or reactivation of transposable elements (TEs). In this context, the role of nutrition-related epigenetic changes on TE activity has become one of the fundamental research areas of environmental epigenomics. Pioneering studies by Wolf et al. (Wolff et al., 1998), Morgan et al. (Morgan et al., 1999), and Waterland and Jirtle (Waterland and Jirtle, 2003) have paved the way for the emergence of environmental epigenomics as a productive research area. These studies have shown that maternal diets supplemented with methyl donors such as folic acid, choline, and betaine lead to a change in fur color from yellow to brown in agouti mouse pups. Researchers have revealed that the molecular basis of this phenotypic change lies in a change in the DNA methylation status of a transposon element located upstream of the agouti gene. Subsequent studies have contributed to the development of the discipline of nutritional epigenomics as a subfield of environmental epigenomics, focusing on the effects of dietary factors (micronutrients, macronutrients, and non-nutritional dietary components) on epigenetic regulation and disease risk (Jiménez-Chillarón et al., 2012). Furthermore, additional evidence regarding transposon suppression through diet-dependent epigenetic mechanisms has emerged in this process.

In this context, Dolinoy et al. investigated the epigenetic consequences of bisphenol A (BPA) exposure in mice and showed that BPA exposure led to significant phenotypic changes such as yellow fur phenotype, obesity, diabetes, and tumor development. The study emphasized that BPA exposure reduced DNA methylation in nine CpG regions located in the cryptic promoter region of the Avy IAP retrotransposon. However, it has been reported that maternal methyl donor or genistein supplementation reverses this BPA-induced hypomethylation and leads to a return to the pseudoagouti phenotype with higher methylation levels in offspring exposed to BPA (Dolinoy et al., 2007).

Another important nutrition-related epigenetic regulatory factor is biotin. Studies in human and mouse cell lines have shown that covalent binding of biotin to the lysine-12 position of histone H4 (H4K12bio) via holocarboxylase synthetase (HCS) plays a role in the repression of LTR retrotransposons (Zempleni et al., 2009). This repressive effect has been determined to be dependent on crosstalk between H4K12bio and DNA methylation markers. Researchers have presented a model suggesting that three nutrition-dependent epigenetic marks—cytosine methylation, H4K12bio, and H3K9me2—function synergistically in the repression of LTR retrotransposons. Furthermore, Kuroishi et al. clearly demonstrated that biotinylation is a natural histone modification, albeit rare in humans (Kuroishi et al., 2011).

Additional evidence regarding the relationship between diet, epigenetic regulation, and disease risk was provided by Agodi et al. (Agodi et al., 2015). In this study, a dietary pattern characterized by low fruit consumption and folate deficiency, and poor adherence to the Mediterranean diet, was shown to be associated with LINE-1 hypomethylation and increased cancer risk in a cohort of 177 healthy women. Similarly, Barchitta et al. examined the relationship between adherence to the Mediterranean diet and particulate matter (PM10) exposure and LINE-1 methylation in a sample of 299 healthy women and reported that monthly PM10 exposure levels were significantly and inversely associated with LINE-1 methylation (Barchitta et al., 2018). In contrast, LINE-1 methylation was shown to exhibit a significant and positive association with the Mediterranean Diet Score. When the studies discussed in this section are considered together, it is seen that transposable elements are not absolutely silent structures within the genome; they are dynamic elements sensitive to environmental conditions, physical and chemical stressors, and metabolic state. While radiation types and chemical exposures weaken the epigenetic mechanisms involved in the suppression of transposable elements, paving the way for their reactivation; environmental factors such as nutrition can play a balancing or suppressive role in TE activity through the same epigenetic networks. This

suggests that TE regulation is not a one-way process, but rather operates in a state of equilibrium that is constantly readjusted by environmental signals. Therefore, transposons are not only TE activity should be considered not only as potential sources of genomic instability, but also as sensitive indicators bearing the traces of environment-genome interaction. This perspective places the evaluation of TE activity within the context of environmental exposures and lifestyle factors within an important framework for understanding genome dynamics.

4. Interaction Between Transposable Elements and Non-Coding RNAs: A miRNA and lncRNA Perspective

The activity of transposable elements (TEs) within the genome is regulated in a multifaceted way, not only through classical epigenetic mechanisms such as DNA methylation and histone modifications, but also through non-coding RNAs. In particular, microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) play central roles in the repression, reactivation, and acquisition of genomic function of TEs. Recent evidence reveals that the relationship between TEs and non-coding RNAs constitutes an evolutionarily shaped, reciprocal, and dynamic regulatory network rather than a unidirectional repression mechanism.

The role of non-coding RNAs in TE regulation can be considered on two main levels. On the one hand, TEs contribute to the emergence of these RNA classes by providing sequential and structural resources in the evolution of miRNA and lncRNA genes; On the other hand, the resulting non-coding RNAs serve to maintain genomic stability by controlling TE expression at the post-transcriptional and chromatin levels. This bidirectional interaction suggests that genome evolution proceeds not through a passive silencing process, but through regaining function and generating regulatory diversity. This section will first address the evolution of TE-derived microRNAs and their regulatory roles on TE activity; then, the functions of lncRNAs in heterochromatin formation, directing epigenetic silencing complexes, and TE control will be discussed in detail.

Transposable Elements and microRNAs: Origin, Evolution, and Reciprocal Regulation

Transposable elements (TEs) are considered not only as structural and mobile DNA components within the genome, but also as sequence resources that play an active role in the evolution of regulatory RNA networks. In this context, the relationship between the evolution of microRNAs (miRNAs) and TEs stands out as one of the important mechanisms explaining the emergence of genomic innovation and regulatory diversity. The pioneering work carried out by Piriyapongsa et al. revealed that a significant portion of the human miRNA repertoire

originates from transposable elements and showed that TEs directly contribute to the evolution of miRNA genes (Piriyapongsa et al., 2007).

In this study, it was shown that sequences derived especially from LINE, SINE, and LTR elements can form hairpin structures specific to miRNA precursors, and these structures can be processed by Drosha–Dicer pathways and converted into mature miRNAs. The palindromic and repeating structures of TE sequences facilitate the formation of secondary structures necessary for miRNA biogenesis, making TEs suitable raw materials for miRNA evolution. Piriyapongsa et al. reported that TE-derived miRNAs tend to be evolutionarily younger and mostly become part of primate-specific regulatory networks. This finding suggests that TE activity may play a role in the species-specific expansion of the miRNA repertoire. This evolutionary framework regarding the TE–miRNA relationship has been supported by bioinformatic analyses conducted by Smalheiser and Torvik. The researchers revealed that numerous miRNA precursors in the human genome exhibit significant overlaps with repetitive sequences, particularly SINE and LINE derivatives, suggesting that TEs have a non-random contribution to the origin of miRNA genes (Smalheiser and Torvik, 2005). These findings demonstrate that TEs are not merely passively present sequences in the genome, but evolutionary reservoirs that support the emergence of novel regulatory RNAs. Experimental studies have also revealed the functional importance of TE-derived miRNAs. Borchert et al. showed that some human miRNAs are directly transcribed from Alu and LTR elements and that these miRNAs can repress the expression of target genes (Borchert et al., 2006). These results reveal that TE-derived miRNAs play an active role not only in biogenesis but also in functional gene regulation. Therefore, miRNAs derived from TEs are considered functional regulatory molecules in the genome that are conserved under selective pressure. However, the TE–miRNA relationship is not limited to a one-way evolutionary process. Subsequent studies have shown that miRNAs can also directly target and repress TE activity. It has been reported that some miRNAs contain sequences complementary to TE transcripts, thereby limiting the expression of LINE and SINE elements (Smalheiser and Torvik, 2006). This suggests that miRNAs may function as a post-transcriptional defense layer protecting the genome against TE-induced instability. In particular, it is suggested that evolutionarily young and species-specific miRNAs exhibit more selective repression profiles towards specific TE families. When all these findings are considered together, it is understood that there is a dynamic and reciprocal regulatory network between transposable elements and miRNAs. TEs provide a sequential and structural source for the emergence of miRNA genes; while the emerging miRNAs contribute

to the limitation of TE activity over time, thus serving to maintain genomic stability. This bidirectional interaction necessitates a reassessment of the role of TEs within the genome, not merely as "parasitic" elements that need to be repressed, but as active actors in the evolution of regulatory RNA networks. In conclusion, the miRNA–TE relationship reveals that genome evolution possesses a multi-layered regulatory architecture shaped by processes of mutual adaptation and gain-of-function, rather than a simple host-parasite conflict. Transposable elements contribute to the expansion of the miRNA repertoire, while these miRNAs create a novel control mechanism through which the genome can regulate its own mobile elements.

The Relationship of Transposable Elements with Heterochromatin and lncRNA Linkage

Heterochromatin represents densely packed chromatin regions that play a fundamental role in maintaining the structural integrity of the genome and regulating gene expression. Transposable elements (TEs) are among the typical and dominant components of heterochromatin, and their presence in these regions is closely related to both epigenetic regulatory mechanisms and genome stability. Disruption of heterochromatin structure can lead to a decrease in the epigenetic repression of TEs, triggering various pathological processes such as aging, cancer, and neurological diseases.

While it is difficult to establish a direct causal relationship between heterochromatic TE duplications and diseases, recent studies have provided strong evidence supporting this connection. It is known that there is a close relationship between chromatin organization during interphase in the cell nucleus and cellular physiological processes. In this context, it is suggested that disruptions in the three-dimensional chromatin architecture of the nucleus can alter cellular responses to environmental stressors and contribute to the emergence of diseases.

Laminopathies, a heterogeneous group of diseases, result from dysfunctions of LAMIN proteins, which ensure the correct interaction of heterochromatin with the nuclear membrane (Solovei et al., 2013). Heterochromatin relaxation and the resulting decrease in TE suppression have been associated with neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and tauopathies (Prudencio et al., 2017; Frost et al., 2014). Although the precise role of TEs in tauopathies is not yet fully understood, it is suggested that HERVK elements are activated by heterochromatin relaxation and that this may trigger neuronal cell death (Sun et al., 2018). Indeed, studies conducted in a Drosophila tauopathy model have shown that the Tau protein dysregulates TEs located within heterochromatin, and these findings have been reported to be consistent with similar mechanisms observed in mammals (Sun et al., 2018). Furthermore,

increased cellular motility during cancer metastasis in different cell types has been shown to be associated with global chromatin compression (Gerlitz, 2020). Similarly, loss of heterochromatin during aging leads to reactivation of TEs, increasing genomic instability and triggering inflammatory responses (Andrenacci et al., 2020). These findings, although needing further experimental data, suggest that heterochromatic TE duplications play an active role in the emergence of specific pathological phenotypes. As highlighted in previous studies, the presence of reversed repeat ends and the tendency for local transposition can increase the susceptibility of Class II TEs to small RNA-mediated silencing mechanisms, thus supporting the formation of heterochromatic islands (Grewal, 2007). This perspective suggests that large heterochromatic blocks may have arisen through regional accumulation of TEs during the evolutionary process. Furthermore, the transformation of some initially euchromatic genomic regions into heterochromatic structures over time can also be explained by this mechanism (Caizzi et al., 2016).

The tendency of TEs to accumulate in certain "preferred" genomic target regions partially explains the TE enrichment observed in heterochromatin. This leads to differences in TE composition at the taxonomic level and causes certain TE classes to become dominant within heterochromatin. For example, while LTR retrotransposons constitute the most common TE class in plant genomes, LINE elements are concentrated particularly in heterochromatic regions in mammalian genomes (Bennetzen et al., 2014; Kazazian, 2000; Graham and Boissinot, 2006). In plants, retrotransposons function as the primary source of heterochromatin replication and are associated with high DNA methylation levels in all cytosine contexts. In addition, histone modifications such as H3K9me2 and H3K27me1 play a critical role in maintaining compact chromatin structure (Vergara et al., 2017).

In the study conducted by Jiang et al., the effects of histone modifications on TEs located in tissue-specific genes were comprehensively investigated. Correlation analyses between mRNA expression and H3K27ac and H3K4me3 peak activity revealed that H3K27ac showed a stronger association with gene expression compared to H3K4me3. Furthermore, it was determined that 1.45% of TEs overlapped with H3K27ac or H3K4me3 peaks, and the vast majority of these TEs showed tissue-specific activity. In particular, LTR4C_SS, a TE subfamily containing binding motifs for SIX1 and SIX4, was reported to be specifically enriched at H3K27ac peaks in adult and fetal ovarian tissues. RNA-seq analyses analyze genes in either exon or promoter regions.

The study revealed that TEs were widely expressed and that a transcript containing 4,688 TEs was specific to the developmental stage or tissue. Remarkably, a transcript containing 1,967 TEs was found to be enriched in testicular tissue. In the porcine dataset, the long terminal repeat (LTR) MLT1F1, which functions as a testis-specific alternative promoter in the SRPK2 gene, a cell cycle-related protein kinase, was identified. The fact that this element is also conserved in human and mouse genomes suggests that TEs in testis-specific genes reflect either an ancient integration event or parallel evolutionary processes (Jiang et al., 2024).

The Relationship Between Long Non-Coding RNAs and Transposable Elements

Long non-coding RNAs (lncRNAs) represent a class of genes that, while not possessing significant protein-coding potential, share many structural and functional features seen in protein-coding genes, such as alternative splicing and evolutionary conservatism (Derrien et al., 2012). LncRNAs are one of the RNA groups with the most pronounced interactions with transposable elements (TEs) in terms of their genomic contributions. Studies have reported that 83% of lncRNAs contain at least one TE, and 42% of the base pairs comprising total lncRNA sequences are of TE origin. In contrast, only 6% of protein-coding genes have been shown to overlap with TE sequences (Kelley and Rinn, 2012; Kapusta et al., 2013).

Although lncRNAs are reduced in some TE classes (e.g., L1) and enriched in others (e.g., MIR), they generally exhibit a distribution close to the frequencies of TEs in the genome (Kapusta et al., 2013). LncRNAs have been shown to play a critical role in embryonic stem cell function, and a large proportion of these lncRNAs are of TE origin. For example, the LINC-ROR lncRNA, which regulates reprogramming activity, consists almost entirely of TE sequences, and its transcription starting point is located within the HERVH element. LINC-ROR RNA contains MLTIJ, L3, MIR, and other TEs, while numerous MIRs, Alus, and other TEs are also found in its intron regions (Kelley and Rinn, 2012; Loewer et al., 2013). LINC-ROR acts as a “miRNA sponge” by preventing miRNA-mediated degradation of critical factors for pluripotency such as OCT4, SOX2, and NANOG (Wang et al., 2013). Interestingly, four predicted miRNA binding sites are located within TE-derived sequences, including experimentally validated miRNA-145 binding sites.

The mouse lncRNA Trp53cor1 (lncRNA-p21) contains seven different TEs that exhibit negative effects on the reprogramming process (Bao et al., 2015). Human L1TD1, derived from an open reading frame of LINE L1, has been identified as an lncRNA necessary for maintaining pluripotency. L1TD1 has been reported to modulate OCT4 levels by interacting with the

pluripotency-regulating factor and RNA-binding protein LIN28A (Narva et al., 2012). However, it has also been shown that this lncRNA is indispensable in mice (Iwabuchi et al., 2011).

Genome-wide single-cell expression analyses have revealed that lncRNAs are extensively modulated in the reprogramming process. In these studies, two lncRNAs, Gm16096 (Ladr49) and 4930500J02Rik (Ladr83), play a critical role in reprogramming and both contain TE sequences (Kim et al., 2015). Similarly, many other lncRNAs involved in maintaining embryonic stem cell status are also TE-derived (Guttman et al., 2011).

However, exceptions exist. For example, the critical pluripotency genes Pou5f1 and Nanog, while possessing SINE elements in the 3′ UTR regions of both human and mouse genomes, avoid TE sequences in their exon regions. This indicates that TE–lncRNA interactions are selectively regulated based on binding and gene function.

In conclusion, the interaction between transposable elements (TEs) and non-coding RNAs reveals that the genome is not merely a passive repository of information, but rather a dynamic and regulatory system shaped throughout evolutionary processes. MicroRNAs and long non-coding RNAs (lncRNAs), by deriving from or targeting TE-derived sequences, not only contribute to maintaining genomic stability but also enable the evolutionary emergence of novel regulatory networks and cell-type-specific transcriptional programs. This reciprocal interaction necessitates moving beyond the classical view of TEs as passive and potentially harmful genetic elements and repositioning them as active components in shaping epigenetic regulation through the evolution of non-coding RNA networks. Thus, the TE–miRNA–lncRNA axis offers a critical conceptual framework for understanding genomic function.

5. Targeting and Integration Site Selection of Transposable Elements

The integration behavior of transposable elements (TEs) within the genome reflects a complex targeting mechanism driven by specific sequential and chromatin characteristics, rather than a purely random process. Studies conducted by Sultana et al. have revealed that TEs exhibit significant variability in their integration site preferences through approaches based on the combined use of deep sequencing techniques and classical molecular methods. These preferences are observed across a wide spectrum, ranging from specific nucleotide motifs to broad chromatin regions and particular chromosomal areas (Sultana et al., 2017).

In this context, two conceptual categories are proposed to define the integration behavior of TEs. “Local-specific elements” describe TEs that integrate consistently at the same position and nucleotide sequence in the genome, while “scattered elements” refer to TEs that exhibit a wider and relatively random distribution across chromosomes, even if they have a specific sequential or regional preference.

Since the choice of integration site directly determines the extent of TE genetic effects, potential pathogenicity risk, and the replication capacity of individual TE copies, understanding the mechanistic and evolutionary dimensions of this process is fundamental to understanding TE–host genome relationships.

Mapping De Novo Integrations

To investigate the mechanisms underlying integration site preference, minimizing the effects of post-integration selection pressures is crucial. Therefore, it is necessary to detect and analyze newly emerging de novo integrations as early as possible, rather than endogenous and evolutionarily old insertions. Lander et al. emphasized the importance of this approach by revealing the distinct distribution patterns of long-spaced element 1 (LINE-1) retrotransposons and non-autonomous short-spaced elements, Alu sequences, in the human genome. The study showed that endogenous L1 and Alu sequences are enriched in contrasting DNA isochords; L1 elements are concentrated in AT-rich regions, while Alu sequences are concentrated in GC-rich regions (Lander et al., 2001).

The non-coding nature of Alu elements and their mobilization in the trans state by the L1 retrotransposition mechanism are considered one of the possible reasons underlying common integration site preferences. Indeed, Wagstaff et al. demonstrated that experimentally induced de novo Alu insertions occur in the same AT-rich isochords as endogenous L1 elements (Wagstaff et al., 2012).

Retrotransposon and Retroviral Integration Profiles

Brady et al. investigated the integration targeting of human endogenous retrovirus type K using HERV-KCon, a reconstructed consensus form of the virus. In this study, HERV-KCon was shown to preferentially integrate into transcription units, gene-rich regions, and near regulatory regions associated with active transcription units. These findings reveal that the integration preferences of transposable elements of retroviral origin are closely related to chromatin activity (Brady et al., 2019).

The target specificity of retroviral integration is largely determined by the interactions of the integrase enzyme with host cell proteins. Studies, particularly on HIV-1, have shown that chromatin-binding factors such as LEDGF/p75 play a central role in directing integration to active gene regions (Schröder et al., 2002; Ciuffi and Bushman, 2006). Similar mechanisms are thought to apply to endogenous retroviruses as well, and the concentration of HERV-KCon integrations in transcriptionally active chromatin regions supports this view. These observations are also supported by genome-wide integration analyses. Studies based on large-scale mapping of retroviral DNA integration have revealed that integration is not a random process; rather, different retroviruses prefer specific genomic and epigenetic features. Genome-wide analyses have shown that HIV-1 tends to integrate predominantly within actively transcribed gene bodies, while gammaretroviruses such as murine leukemia virus (MLV) prefer transcription start regions and areas close to promoters (Bushman et al., 2005). These different integration profiles suggest that specific protein-protein interactions established by retroviral integrases with host chromatin are decisive in integration targeting. In the same study, it was reported that integration regions exhibited strong correlations with nucleosome density, DNA accessibility, and histone modifications. Specifically, regions with open chromatin structures, DNase I-sensitive regions, and histone markers associated with active transcriptional status have been shown to constitute favorable targets for retroviral integration (Bushman et al., 2005). These findings reveal that retroviral integration is not solely a DNA sequence-dependent process; chromatin architecture and epigenetic context play a central role in integration site selection. This genome-wide perspective also provides a strong framework for explaining the integration preferences observed in endogenous retrovirus models such as HERV-KCon. HERV-KCon's integration profile, concentrated in gene-rich and transcriptionally active regions, suggests that evolutionarily diverse retroviral elements can "read" common chromatin features and develop integration strategies compatible with the functional architecture of the host genome. In this context, understanding the integration preferences of evolutionarily young and potentially reactivable endogenous retroviruses such as HERV-K is important not only from the perspective of genome evolution but also for assessing the risks associated with gene regulation, cellular stress responses, and pathological processes. Comparative analysis of retrotransposon and retroviral integration profiles allows for the different interaction strategies of mobile genetic elements with the host genome and provides a foundation for interpreting the functional consequences, which will be discussed in later sections. Furthermore, the integration profiles of retroviral elements are also important in terms of potential biological consequences. Integrations occurring near genes or around regulatory elements can lead to disruption of gene

expression, the formation of alternative transcription initiation points, or epigenetic reprogramming. Indeed, both experimental retroviral vector studies and endogenous retrovirus analyses have shown that integration sites can have long-term effects on cellular gene regulation (Mitchell et al., 2004).

Biotechnological and Therapeutic Use of Targetable T-Cells

The ability to stably integrate into the host genome forms the basis for the use of transposable elements as biotechnological tools. This feature creates a wide range of applications, from functional genomics studies to gene therapy. Retrovirus-derived vectors are frequently preferred due to their capacity to provide effective gene transfer and long-term gene expression. Their high integration efficiency, particularly in dividing cells, makes these vectors attractive for target cell populations such as hematopoietic stem cells (Cavazzana-Calvo et al., 2000; Naldini, 2015).

However, this approach also brings with it serious biosafety issues. In a study conducted by Hacein-Bey-Abina et al. on patients with X-linked severe combined immunodeficiency (SCID-X1), it was observed that some patients who underwent retroviral gene therapy developed uncontrolled T-cell proliferation approximately three years after treatment. In these cases, it was determined that retroviral vector integration occurred in regions close to the LMO2 proto-oncogene promoter, leading to abnormal gene expression (Hacein-Bey-Abina et al., 2003). This clearly demonstrates that integration site selection is crucial not only for the efficiency of gene transfer but also for long-term clinical safety.

These clinical experiences have necessitated the development of new strategies to make integration profiles more predictable and safe. In this context, approaches to redirecting the integration tendencies of retroviral vectors or using alternative mobile genetic elements have come to the forefront. DNA transposons, particularly due to their simpler structures, narrower integration preferences, and modular redesignability, offer attractive alternatives in biotechnological applications (Ivics et al., 1997).

The Sleeping Beauty (SB) DNA transposon system is a reactivated Tc1/mariner type transposon characterized by its integration being necessarily dependent on TA dinucleotides. Early molecular and genome-wide studies have shown that this target specificity is related to the structural features of DNA, and that SB integrations do not show significant enrichment in promoters and transcription start regions (Vigdal et al., 2002; Yant et al., 2005). This integration profile contributes to a lower risk of insertional mutagenesis compared to retroviral vectors.

Following the identification of these biological features, the controlled and relatively safe integration profile of the SB system has enabled its effective use in functional genomics applications. Indeed, Copeland et al. used the SB transposon system in advanced genetic screening approaches in mouse models, enabling the identification of novel genes involved in oncogenesis (Copeland et al., 2009). These transposon-based studies have contributed to the functional elucidation of tumor suppressor genes and oncogenes in vivo and have provided an important framework for the functional interpretation of cancer genomes. Furthermore, the capacity of DNA transposon systems to provide stable gene integration in human cells allows these elements to be evaluated as alternative gene transfer platforms to viral vectors. In particular, hyperactive transposase variants obtained by reconstitution of the Sleeping Beauty transposon system have been shown to generate highly efficient and persistent gene integration in human and other vertebrate cells. This feature makes it possible to widely use transposon-based approaches in functional genomics studies, gene regulatory network analysis, and experimental gene modification strategies (Mátés et al., 2009).

In conclusion, the targetability characteristics of transposable elements offer a broad biotechnological potential ranging from the systematic analysis of gene function to the development of safe gene therapy approaches. However, the safe transfer of this potential to clinical applications depends on a detailed understanding of the molecular basis of integration site selection and the development of targeted integration strategies. Therefore, controlling the integration profiles of TE-based vectors remains one of the most critical focuses of modern gene therapy and functional genomics research.

Molecular Mechanisms and Structural Basis of Integration

It has been shown that retroviral integration profiles can be redirected through molecular engineering approaches via fusion proteins that combine integrase-binding domains (IBD) with chromatin-recognizing DNA-binding domains. In one of the pioneering studies in this field, Ferris et al. demonstrated that lens epithelium-derived growth factor (LEDGF/p75)-based fusion proteins can redirect HIV-1 DNA integration to genomic regions different from their natural targets in the host genome. This finding showed that integration site selection is strongly dependent not only on the intrinsic properties of viral integrase but also on the interactions established with host cell proteins (Ferris et al., 2010).

The C-terminal region of the LEDGF/p75 protein contains the binding domain that enables direct interaction with integrase, while the N-terminal region functions as a chromatin-binding domain. Under natural conditions, LEDGF/p75 predominantly directs HIV-1 integrations to actively transcribed gene bodies. However, replacing the chromatin-binding domains of LEDGF with different chromatin-recognizing modules, such as the PHD finger derived from the ING2 protein or the HP1α chromodomain, significantly altered the target specificity of HIV-1 integrations. These experimental approaches are of great importance as they demonstrate that integration site selection exhibits a modular structure and can theoretically be reprogrammed (Ferris et al., 2010).

Similarly, the integration preferences of murine leukemia virus (MLV) and MLV-based vectors are determined by the specific interactions that the viral integrase establishes with the BET protein family (BRD2, BRD3, and BRD4) in the host cell. De Rijck et al. demonstrated through genome-wide integration analyses that MLV integrations are significantly enriched near active promoters and transcription start sites, and that this targeting occurs via BET proteins (De Rijck et al., 2013). It has been reported that when this interaction with BET proteins is disrupted, integrations move away from promoter regions and exhibit a more diffuse distribution across the genome. These findings clearly demonstrate that integration site selection is determined by direct protein-protein interactions between viral proteins and host chromatin regulators.

The structural basis of retroviral integration occurs via high-order nucleoprotein complexes called “intasomes.” These complexes, containing HIV-1 integrase, viral DNA ends, and host DNA, are key structural units that determine both the specificity and efficiency of the integration reaction. Passos et al. obtained high-resolution cryo-electron microscopy structures of the HIV-1 strand transfer complex using soluble integrase fusion proteins. These structural studies have elucidated the interaction surfaces of integrases with DNA, the organization of catalytic centers, and the conformational changes that occur during integration in detail (Passos et al., 2017).

Elucidating the high-resolution structural features of supramolecular complexes that drive the integration of transposable elements (TEs) is critical for understanding these processes at the molecular level. Studies have shown that the architecture of protein-DNA complexes involved in TE integration can be determined with high accuracy by using X-ray crystallography and cryo-electron microscopy (cryo-EM) together. These holistic structural approaches allow for the identification of interaction networks that determine the selection of integration sites and also enable a more detailed examination of the dynamic relationships between host chromatin

and integration complexes. The high-resolution structural data obtained have been supported by relevant studies (Maskell et al., 2015; Yin et al., 2016; Ballandras-Colas et al., 2016; Ballandras-Colas et al., 2017; Passos et al., 2017), which facilitate the development of novel and more specific targeting strategies for guiding TE integration.

Consequently, the selection of integration sites for transposable elements and retroviral vectors relies on a multilayered regulatory process encompassing sequence preferences, chromatin context, specific interactions between viral and host proteins, and the structural features of high-order nucleoprotein complexes. Understanding the molecular and structural basis of integration mechanisms not only elucidates the roles of TEs in genome evolution but also enables the development of safer, more predictable, and targeted integration strategies for gene therapy and functional genomics applications.

6. The Silent Majority of the Genome: Transposable Elements and Their Intersection with Disease

Although the structural and functional organization of the human genome has for many years been largely defined through protein-coding genes, transposable elements (TEs), which make up approximately 45% of the genome, have radically changed this classical perspective. For many years, transposable elements were considered ‘selfish DNA’ or ‘dysfunctional genomic load’; this view was particularly championed by Doolittle and Orgel. In contrast, Barbara McClintock suggested that these elements could assume functional roles in genomic response and adaptation processes. Today, TEs are recognized not only as a source of genomic instability but also as dynamic elements that play an active role in gene regulation, chromatin architecture, and cellular adaptation processes. Transposable elements are basically divided into two main classes: retrotransposons and DNA transposons. Retrotransposons, which are dominant in the human genome; LINE (Long Interspersed Nuclear Elements), SINE (Short Interspersed Nuclear Elements), and endogenous retroviruses (ERVs) are among the subgroups included. LINE-1 (L1) elements, in particular, are at the center of disease-related studies because they are one of the few transposons in the human genome that still retain the ability to retroposition. Although the majority of DNA transposons in the human genome have been evolutionarily inactivated, their historical role in shaping genomic architecture cannot be ignored. The capacity of TEs to move within the genome can directly influence gene function through various mechanisms such as insertion mutagenesis, gene deconstruction, alteration of alternative splicing patterns, and chromosomal rearrangements. However, the influence of TEs is not limited to physical translocation. TE sequences can function as regulatory elements such as

promoters, enhancers, silencers, and insulators, thus shaping the tissue-specific or developmental expression of neighboring genes. With these characteristics, TEs are considered an important resource in the evolution of gene regulation networks.

At the cellular level, TE activity is normally tightly controlled by DNA methylation, histone modifications, and small RNA-mediated silencing mechanisms. However, when this epigenetic balance is disrupted as a result of aging, environmental stressors, infections, or genetic predispositions, TEs have been shown to be reactivated. Studies reveal that this loss of control is associated with numerous human pathologies such as cancer, neurodegenerative diseases, autoimmune disorders, and neurodevelopmental disorders.

In particular, in cancer biology, TE activation has been shown to be associated with genomic instability, contribute to tumor heterogeneity, and influence immune responses in the tumor microenvironment. Similarly, in nervous system diseases, increased TE expression has been associated with neuronal genome mosaicism, cellular stress responses, and inflammatory processes. In autoimmune and inflammatory diseases, the expression of endogenous retroviral elements is among the potential triggering factors in the misdirection of the immune system. However, the relationship between transposable elements (TEs) and diseases should not be evaluated in a one-sided and purely pathogenic framework. It is known that some TE-derived sequences have been domesticated (exapted) by the host genome during the evolutionary process and assume critical roles in fundamental biological processes such as immune response, placental development, or nervous system functions. This demonstrates that the roles of TEs in human health and disease are complex, context-dependent, and multifaceted. Transposable elements (TEs) function not only as passive sequences in the human genome but also as dynamic elements that can create profound effects at the genetic and epigenetic levels. The contribution of TEs to disease pathogenesis largely depends on the way they are inserted into the genome and the consequences of these insertions on gene structure and gene regulation. In particular, TE insertions occurring in the germline can play a decisive role in the emergence of hereditary diseases. Such insertions can occur de novo in the affected individual, or they can be found as a stable insertion allele passed down through generations and can exhibit inheritance patterns similar to classic monogenic diseases.

The insertion of TEs into genic regions or regulatory elements of genes leads to structural changes that can directly disrupt gene function. These changes include interruption of the coding sequences of genes, premature termination of transcription, or triggering of alternative

RNA processing processes. In particular, exonization, resulting from the recognition of TE sequences as exons, often causes a shift in the reading frame and results in the formation of a high percentage of premature stop codons. Such molecular disruptions lead to shortening or complete non-functionality of the gene product, resulting in loss-of-function phenotypes (Burns, 2020).

In addition, TE insertions can also trigger gain-of-function effects, although these are rarer. For example, a TE carrying strong promoter or enhancer-like sequences can cause the inappropriate expression of neighboring genes at inappropriate times or in the wrong tissues. This can disrupt cellular homeostasis and predispose to disease development. Therefore, transposable elements (TEs) are associated with diseases not only as sources of mutations but also as elements that reshape gene regulatory networks. Consequently, genomic insertions of transposable elements contribute to the emergence of human diseases through multiple mechanisms such as gene destruction, alteration of RNA processing, and dysregulation of gene expression. With these characteristics, TEs stand out as important genomic factors that should be considered in a wide spectrum of diseases, from monogenic diseases to complex multifactorial pathologies. This section aims to systematically examine the relationship between transposable elements and human diseases in light of current literature, based on their molecular properties and genomic behavior. In the following sections, major disease groups will be discussed under separate headings; the molecular mechanisms of TE activity for each disease will be discussed, supported by experimental and clinical findings. Thus, it will be shown that TEs are not merely genomic remnants but important biological actors in understanding human diseases and developing future diagnostic and treatment strategies.

Transposon-Related Splicing Disorders and X-Linked Dystonia-Parkinsonism Pathogenesis

Transposon (TE) insertions can significantly alter mRNA splicing processes, leading to abnormal alternative splicing events such as exon skipping or intron insertion. Such splicing disorders can affect the regulation of gene expression, resulting in various disease phenotypes. For example, the insertion of the retrotransposon element SVA (SINE–VNTR–Alu) into an intron of the TATA box-binding protein-related factor 1 (TAF1) gene has been associated with X-linked dystonia-parkinsonism (XDP), a rare movement disorder specific to the Philippines (Aneichyk et al., 2018).

Integration of the SVA element into the intronic region disrupts the normal splicing process of TAF1 gene mRNA, specifically resulting in the insertion of intron 32. This abnormal splicing event forms the molecular basis of the disease by reducing the production of functional TAF1 transcripts (Aneichyk et al., 2018). However, XDP pathogenesis is not limited to SVA splicing alone; it has been shown that the population contains alleles with variable repeat lengths, exhibiting variable length expansions of the hexanucleotide repeat sequence (CCCTCT)n(\mathrm{CCCTCT})_n(CCCTCT)n within the SVA element. A strong correlation exists between the length of this hexanucleotide repeat and the age of disease onset; longer repeat sequences are associated with earlier onset of clinical symptoms (Bragg et al., 2017). Although the precise role of repeat length in pathogenesis is not yet fully elucidated, it is thought to affect the efficiency of retroelement transcription and promote the formation of secondary DNA structures known as G-quadruplexes by increasing guanine stacking (Bragg et al., 2017).

Molecular Pathogenesis of FOXF1 Regulatory Region Disorders and Alveolar Capillary Dysplasia

Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV; MIM #265380) is a rare and severe developmental lung disease occurring in approximately 1 in 100,000 births (Bishop et al., 2011; Galambos et al., 2015; Slot et al., 2018). Newborns with ACDMPV frequently develop progressive hypoxemic respiratory failure and severe pulmonary arterial hypertension (PAH); this may be accompanied by additional congenital anomalies of the cardiovascular, gastrointestinal, and genitourinary systems. Most affected infants are born at full gestational age and normal birth weight, but clinical signs appear within the first 24–48 hours of life, and the disease usually results in death within the first month. Studies into the molecular etiology of ACDMPV have revealed that haploinsufficiency of the FOXF1 gene is one of the primary causes of this fatal neonatal lung developmental disorder. In particular, heterozygous copy number variations (CNVs) involving regulatory regions of the FOXF1 gene play a critical role in the pathogenesis of the disease. Szafranski et al. (2016) identified two similar heterozygous deletions involving the FOXF1 enhancer region. In one of these cases, deletion of the enhancer region located in the maternal allele was shown to lead to pulmonary hypertension and misalignment of the pulmonary veins without typical ACD histopathological findings. In another case, it was reported that a booster deletion in the paternal allele was associated with the classic ACDMPV phenotype, which is characterized by expected neonatal

lethality. In addition, non-coding single nucleotide variants (SNVs) affecting FOXF1 gene expression have also been shown to play a role in shaping the disease phenotype. The functional effect of a non-coding variant, rs150502618, was evaluated by cloning the FOXF1 promoter into the report plasmid; it was found that the A allele increased promoter activity approximately 2.5-fold compared to the common G allele (Szafranski et al., 2019). This increase was consistent with the higher-than-expected FOXF1 transcript levels observed in the lung biopsy sample of the patient. Electrophoretic mobility shift analyses (EMSA) have shown that the rs150502618-A variant increases its affinity to a CTCF binding site located in the FOXF1 enhancer region and partially containing the AP-2 binding motif. It is suggested that this may lead to increased FOXF1 transcription by affecting local chromatin architecture and three-dimensional genome organization. Indeed, it has been previously shown that disruptions in topologically related domain (TAD) structure can alter the expression of disease-associated genes, leading to pathogenic outcomes (Spielmann & Mundlos, 2016).

Molecular Pathogenesis of Alu-Mediated Splicing Disorders and Alport Syndrome

Alport syndrome is a genetically heterogeneous basement membrane disorder characterized by progressive renal failure, sensorineural hearing loss, and characteristic ocular lesions. Although the vast majority of cases show an X-linked inheritance pattern, the existence of autosomal recessive forms involving the COL4A3 and COL4A4 genes has also been identified. These genes encode the α3(IV) and α4(IV) chains of type IV collagen, which are critical for the structural integrity of the glomerular basement membrane. One of the important findings regarding the molecular mechanisms of Alport syndrome is the Alu-mediated abnormal mRNA splicing events occurring in the COL4A3 gene. Knebelmann et al. (1995), while analyzing COL4A3 mRNA transcripts in lymphocytes obtained from patients with Alport syndrome, identified an abnormal transcript containing a 74 base pair long insertion at the junction of exon IV and exon V–VI. This insertion was shown to originate from an antisense-oriented Alu element located in the intron V region of the COL4A3 gene. It was determined that this Alu sequence was inserted into mature α3(IV) mRNA by activating a cryptic acceptor insertion site as a result of a single G→T transversion mutation (Knebelmann et al., 1995). Scanning DNA sequence databases revealed that the inserted 74 bp sequence was approximately 85% identical to the complementary sequence of the right half of an Alu element (Alu consensus positions 278–205) (Britten et al., 1988). Structural analysis of COL4A3 genomic clones revealed that an 830 bp intron downstream of exon V contains a single antisense Alu element approximately

108 bp from the 3′ end (Quinones et al., 1992). This Alu element was found to have 81% similarity to the consensus Alu sequence and belonged to class II Alu repeats according to the Britten classification (Britten et al., 1988). These findings clearly demonstrate that Alu elements contribute to the development of autosomal recessive Alport syndrome by disrupting COL4A3 gene function through abnormal splicing.

Alu Insertions in the FGFR2 Gene and Molecular Pathogenesis of Apert Syndrome

Apert syndrome (MIM #101200) is a severe, autosomal dominant developmental disorder characterized by premature closure of the cranial sutures, craniosynostosis, and bilateral fusion of bones in the hands and feet (syndactyly). Less frequently, additional malformations affecting the skin, skeletal system, central nervous system, and other internal organs can also be observed (Upton & Zuker, 1991; Park et al., 1995; Slaney et al., 1996). Apert syndrome is one of five craniosynostosis syndromes associated with allelic mutations in the fibroblast growth factor receptor 2 (FGFR2) gene. Studies into the genetic basis of Apert syndrome have shown that the disease is largely associated with de novo mutations occurring in the FGFR2 gene. Oldridge et al. (1999) demonstrated that Alu element insertions in the FGFR2 gene constitute a specific mechanism in the pathogenesis of the disease. In their study, a C/A polymorphism in intron 7 was identified in Patient 1 (patient: CA; mother: CC; father: AA), and analysis of the DNA segments containing both the polymorphism and the Alu insertion revealed that the Alu element added to intron 7 was of paternal origin. Similarly, in Patient 2, a homozygous structure was detected for intron 7, while heterozygosity was observed for the C/T polymorphism in intron 9. Combined evaluation of the DNA regions containing the polymorphism and the Alu insertion showed that the Alu insertion was in a cis position with the C allele and therefore of paternal origin (Oldridge et al., 1999). These findings revealed that the Alu insertions in both patients developed as a result of de novo mutations occurring in the father's germline. These results are also consistent with the study by Moloney et al. (1996), which showed that the novel mutations seen in Apert syndrome were of paternal origin only and that maternal or somatic transmission was not involved. This indicates that Alu element insertions in the FGFR2 gene constitute a unique and distinctive mechanism in the molecular pathogenesis of Apert syndrome.

Alu Insertion in the FAS Gene and Molecular Pathogenesis of Autoimmune Lymphoproliferative Syndrome

Autoimmune lymphoproliferative syndrome (ALPS; MIM #601859) is a rare immune regulatory disorder characterized by disruption of lymphocyte homeostasis. In patients with ALPS, T lymphocytes show resistance to apoptosis compared to T cells of healthy individuals. Clinically, the disease presents with splenomegaly and lymphadenopathy, an increased number of double-negative ($CD4^{-}CD8^{-}$) T cells, and various autoimmune findings (Sneller et al., 1997).

A large proportion of ALPS cases are associated with mutations in the FAS (Apo-1, CD95, TNFRSF6) gene and are classified as ALPS type 1a; mutations in other genes lead to ALPS types 1b, 2, and 3. Fas protein is a transmembrane signaling protein located on the cell surface, weighing approximately 48 kDa, and plays a key role in initiating programmed cell death (apoptosis). Fas is particularly highly expressed in the double-positive ($CD4^{+}CD8^{+}$) phase of thymocytes and in activated peripheral T and B cells. Mutations in the FAS gene, localized in the chromosome 10p24.1 region in humans, can cause lymphoproliferative diseases and autoimmune phenotypes similar to systemic lupus erythematosus (Rieux-Laucat et al., 1995; Fisher et al., 1995).

One of the rare but noteworthy mechanisms in ALPS pathogenesis is the insertion of Alu elements into the FAS gene. In a study by Tighe et al. (2002), sequence analysis performed using GenBank and RepeatMasker showed that a 281 base pair long Alu repeat element had been inserted into the FAS gene. This Alu insertion contains a 34-base-long poly(A) tail and 17 bases of perfect direct repeats surrounding the insertion element. The insertion sequence was determined to match the Alu-Sb1 SINE consensus sequence with 99.31% (286/288 bp) and a single gap, with the relevant sequence having the GenBank accession number HSU14569. The Alu element in question was found to be an antisense insertion into the FAS gene (Tighe et al., 2002). This retrotransposition event occurs in the intronic region, leading to alternative splicing variations and ultimately disrupting the production of the functional Fas protein, contributing to the development of the ALPS phenotype. These findings suggest that retrotransposon-derived Alu insertions may play a role in the molecular pathogenesis of autoimmune and lymphoproliferative diseases by affecting not only gene-coding sequences but also splicing processes.

Alu Insertion in the OPA1 Gene and Molecular Pathogenesis of Autosomal Dominant Optic Atrophy

Autosomal dominant optic atrophy (ADOA; OMIM #165500) is the most common form of inherited optic neuropathies, with an estimated prevalence ranging from 1:10,000 to 1:50,000 in different populations (Kjer et al., 1996). The disease is characterized by an insidious onset and progressive clinical picture resulting from selective degeneration of retinal ganglion cells. Clinical findings include varying degrees of visual acuity reduction, temporal optic disc pallor, tritanopia, and the development of central, paracentral, or secocentral scotomas (Carelli et al., 2004). Although ADOA exhibits an autosomal dominant inheritance pattern, it is notable for its significant intra- and interfamilial phenotypic variability and incomplete penetrance. The genetic basis of ADOA most frequently involves mutations in the OPA1 gene, which plays a critical role in the regulation of mitochondrial dynamics. Gallus et al. (2010), in their molecular analysis of a family diagnosed with ADOA, sequenced 30 coding exons of the OPA1 gene in DNA samples obtained from the index case and found no known pathogenic point mutations. However, a hemizygous product of approximately 604 bp in length was detected during PCR amplification of exon 8. Cloning and sequencing of this long band revealed the presence of an insertion of approximately 325 bp. BLAST and RepeatMasker analyses were used to determine the molecular nature of the insertion, and it was determined that 289 bp of the inserted sequence belonged to an AluYb8 element; this sequence was reported to have 99.65% homology with the AluSb2 consensus sequence (Jurka et al., 2005; Gallus et al., 2010). The Alu insertion contains a 25 bp poly(A) tail at the 3′ end and 17 bp of perfect direct repeats surrounding the insertion site. This Alu element has been shown to be located in intron 7 of the OPA1 gene, 21 bp upstream of exon 8, and near the acceptor splice site (c.784–21_22). Functional analyses revealed that this Alu insertion leads to exon 8 skipping in OPA1 mRNA, resulting in disruption of the normal OPA1 protein structure (Gallus et al., 2010). These findings suggest that Alu element-mediated retrotransposition events can affect the expression of genes associated with mitochondrial function by disrupting splicing mechanisms and may play a direct role in the pathogenesis of neurodegenerative diseases such as ADOA.

The Role of Transposable Elements in Chronic Granulomatous Disease

Chronic Granulomatous Disease (CGD) is a severe congenital immunodeficiency syndrome resulting from defects in the NADPH oxidase enzyme complex in phagocytic leukocytes. NADPH oxidase is responsible for the production of reactive oxygen species (ROS), which

phagocytes use to kill pathogens. CGD arises from mutations in four different subunits of NADPH oxidase. The most common form is the X-linked form, resulting from mutations in the gp91-phox subunit encoded by the CYBB gene (Roos, de Boer, Kuribayashi, et al., 1996).

A study by Meischl et al. (2000) showed that the heterogeneity seen in clones obtained from patients with CGD resulted from combinations of insertion of intronic LINE-1 (L1) transposon fragments and exon skipping. LINE-1 fragments are located between exons 5 and 6, and the consensus sequences of the active LINE-1 elements have been determined to correspond to nucleotides 5220–5334 and 5220–5372, respectively (Kimberland, Divoky, Prchal, Schwahn, Berger, & Kazazian, 1999). Both LINE-1 fragments contain stop codons within their reading frames, which largely predicts truncated and non-functional protein products. The researchers analyzed XL-PCR products cloned from genomic DNA encompassing intron 5 of the CYBB gene and found an 836 bp truncated and fragmented LINE-1 element (excluding the poly-A tail) located between positions 1880 and 1881 of the intron. It has been observed that when LINE-1 sequences are absent in cDNA, skipping exons 5 and 6 causes a frameshift, resulting in the stop codon appearing 50 nucleotides down. These findings clearly demonstrate the potential effects of transposons on gene regulation and protein synthesis, and their association with genetic diseases (Meischl, de Boer, Ahlin, & Roos, 2000).

The Role of LINE-1 Transposons in Duchenne and Becker Muscular Dystrophies

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are X-linked genetic disorders caused by mutations in the dystrophin gene, which spans a region of approximately 2,500 kb on the X chromosome. The majority of mutations are partial gene deletions (60%) or duplications (6–10%) (Koenig, Hoffman, Bertelson, Monaco, Feener, & Kunkel, 1987; Den Dunnen et al., 1989; Hu, Ray, Murphy, Thompson, & Worton, 1990). Gene analyses have shown that mutations in the dystrophin transcript that conserve the reading frame cause BMD, while mutations resulting in frame loss cause DMD (Monaco, Bertelson, Liechti-Gallati, Moser, & Kunkel, 1988).

In recent years, analysis of dystrophin mRNA has shown that determining the translational reading frame is more reliable than gene analysis for diagnosing DMD/BMD. In particular, in the case of Kobe DMD, exon skipping was observed during a small exon deletion, and it was proven that this occurred during dystrophin mRNA splicing (Matsuo et al., 1991).

Narita et al. (1993) examined the possible deletion regions of the dystrophin gene in DNA samples collected from Japanese DMD patients. The amplification product extending from intron 43 to the middle of exon 44 was found to be of the predicted length (106 bp); however, the amplification product extending from the 5' end of exon 44 to intron 44 was found to be approximately 600 bp longer than it should be. This indicates an insertion at the boundary of exon 44 and intron 44. In DNA sequence database searches, it was determined that this insertion was 98% complementary to the 3' portion (nucleotides 5563–6161) of the consensus sequence of the LINE-1 (L1) element. This L1 insertion led to the skipping of exon 44 during splicing and has been identified as a key mechanism in the development of the DMD phenotype. This finding suggests that LINE-1 transposons may influence DMD/BMD phenotypes by causing functional disruptions in the dystrophin gene (Scott et al., 1987).

The Role of Alu Elements in Fabry Disease

Fabry disease is a congenital defect in glycosphingolipid catabolism caused by mutations in the X-linked gene encoding the lysosomal enzyme alpha-galactosidase A (EC 3.2.1.22). This disease is particularly noteworthy for its genetic rearrangements and transposon-element relationships.

In a study by Kornreich et al. (1990), breakpoints of five partial gene deletions and one partial gene duplication were examined. The affected hemizygous mutant gene was analyzed by cloning and sequencing or by amplifying and sequencing the relevant genomic region using polymerase chain reaction (PCR). Although the alpha-galactosidase A gene contained 12 Alu repetitive elements (representing approximately 30% of the 12 kb gene or a 1 Alu/1 kb ratio), only one deletion resulted from an Alu-Alu recombination. The remaining five rearrangement events involved disordered recombination events with 2–6 base pair short direct repeats at deletion or duplication breakpoints. One of these rearrangements was noted as unusual because it had a 3’ short direct repeat within an Alu element, while another had two deletions of 1.7 kb and 14 bp separated by a 151 bp reverse sequence. These findings suggest that Alu elements play a critical role in genetic rearrangements in Fabry disease and that transposons may be influential in genetic disorders.

The Role of Alu Elements in Familial Hypercholesterolemia

Familial hypercholesterolemia (FH, OMIM 143890) is an autosomal codominant inherited lipoprotein metabolism disorder characterized by elevated circulating total and low-density lipoprotein (LDL) cholesterol levels, the presence of tendon xanthomas, and early atherosclerosis. The genetic basis of FH is mutations in the LDL receptor (LDLR) gene (OMIM 606945). LDLR mutations lead to a deficiency of functional LDL receptors on the cell surface, resulting in increased plasma LDL levels (Goldstein, Hobbs, & Brown, 2001).

Jelassi et al. (2012) performed breakpoint analyses using long-range PCR and sequencing methods to further characterize deletions in the LDLR gene. The study showed that in some patients, the deletion of exons 2–5 covered 12,684 bp (from position 11,205,052 of intron 1 to position 11,217,736 of intron 5) and the deletion of exons 5–6 covered 2,364 bp (from position 11,216,885 of intron 4 to position 11,219,249 of intron 6). Bioinformatic analysis of the breakpoints revealed that these deletions occurred via Alu-Alu homologous recombination. For the deletions of exons 2–5, the relevant Alu sequences were AluSp (11,204,838–11,205,120) in intron 1 and AluSx (11,217,515–11,217,805) in intron 5, both exhibiting antisense orientation. For the deletions of exons 5–6, the relevant Alu sequences were AluSx (11,216,591–11,216,901) in intron 4 and AluSz (11,218,967–11,219,265) in intron 6, both also exhibiting antisense orientation. For both deletions, a new fully recombinant Alu sequence was formed at the mutation breakpoint, demonstrating that this mechanism is intrachromatid non-allelic homologous recombination (NAHR). These findings reveal that Alu elements play a critical role in leading to genetic rearrangements in the LDLR gene and the FH phenotype.

The Role of Alu Elements in Fanconi Anemia

Fanconi anemia (FA) is a rare genetic disorder characterized by developmental abnormalities, bone marrow failure in the first decade of life, predisposition to solid tumors and leukemia, and cellular hypersensitivity to cross-linking agents (Auerbach, 2009). FA results from biallelic mutations in genes encoding proteins critical for DNA cross-linking (ICL) repair. To date, 17 FA genes (FANCA–FANCS) have been identified, and some patients still have unknown causative gene mutations (Kottemann & Smogorzewska, 2013; Sawyer et al., 2015; Wang & Smogorzewska, 2015).

Rickman et al. (2015) performed Sanger sequencing on genomic DNA and cDNA from primary fibroblasts, parental peripheral blood, and lymphoblastoid cell lines (LCLs) in the first genetically affected case in the family and detected compound heterozygous mutations in the UBE2T gene. The paternal deletion (g.202332626_202341295del) may have resulted from recombination between two AluYa5 repeats in the UBE2T gene. Since this deletion leads to the loss of the majority of the gene, including the start codon, a null allele is expected.

The maternal mutation (g.202332626_202341295dup) is also associated with Alu recombination. This mutation resulted from a large duplication of the genomic region between two AluYa5 repeats. Cloning of the cDNA of the first case revealed a transcript containing the putative duplication c.-64_468dup (dupEx2_6). In this transcript, exon 6 is inserted into the duplicated exon 2; the inclusion of the non-coding region from exon 2 resulted in a frameshift and an early stop codon. These findings suggest that Alu elements play a critical role in the emergence of the FA-T phenotype by mediating genetic rearrangements in the UBE2T gene.

FUTURE PERSPECTIVES

Although research on transposable elements has profoundly transformed our understanding of genome dynamics, the field remains far from complete. Transposable elements now occupy a central position at the intersection of epigenetics, developmental biology, environmental genomics, and evolutionary biology, and their relevance is expected to grow further in the coming years.

Advances in single-cell genomics and epigenomics are poised to revolutionize our understanding of TE activity by enabling the resolution of cell-type-, tissue-, and developmental stage–specific transposition dynamics. These approaches will allow researchers to distinguish between pathological TE activation and physiologically regulated expression patterns, particularly during early development, stem cell maintenance, and regenerative processes. In this context, TEs are likely to emerge as key regulatory components rather than passive genomic passengers.

Another critical direction for future research lies in systematically characterizing the relationship between environmental exposures and TE regulation. Factors such as radiation, chemical pollutants, and nutritional status have been shown to modulate epigenetic defense mechanisms, thereby influencing TE repression and reactivation. Elucidating the long-term consequences of environmentally induced TE activity will be essential not only for evolutionary biology, but also for public health and disease prevention. In this regard, TEs hold promise as epigenetic biomarkers reflecting cumulative environmental exposure and genome instability.

From a clinical and translational perspective, the role of transposable elements in complex diseases—including cancer, neurodegenerative disorders, and immune-related pathologies—remains an open and actively debated question. Determining whether TE activation acts as a causal driver or a secondary consequence of disease-associated epigenetic dysregulation represents a major challenge for future studies. At the same time, emerging genome-editing and synthetic biology technologies may enable the controlled exploitation of TE-derived mechanisms for therapeutic and biotechnological applications.

In conclusion, transposable elements are not the “dark matter” of the genome but essential components that shape regulatory networks, drive evolutionary innovation, and mediate genome–environment interactions. Future research will continue to redefine the genome as a dynamic, adaptive system, expanding our understanding of biological complexity.

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