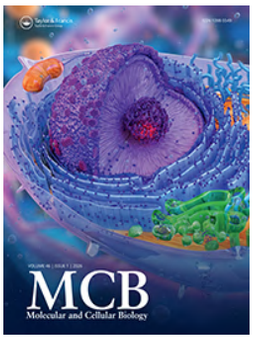

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Impact of Transposable Elements on DNA Double-Strand Break Repair and Genomic Stability

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ABSTRACT

Transposable elements (TEs) are indispensable components of eukaryotic genomes, mechanistically linked to carcinogenesis, aging and other degenerative diseases. The ability of TEs to self-propagate and cause deletions, inversions or insertions within the genome poses a real threat to the fidelity of genomic integrity. This review discusses the fundamental properties of TEs, with a focus on cellular interactions associated with mechanisms involved in recombination, replication, and DNA repair. Since mobilization of TEs induces double-strand breaks (DSBs), faulty repair mechanisms could lead to cellular dysfunction, pathology and death. The TE-induced DNA DSB repair cascade follows either homologous recombination (HR) or non-homologous end-joining (NHEJ) pathways. Importantly, epigenetic regulatory mechanisms including DNA methylation and histone acetylation provide additional control in ensuring accurate DNA repair and could prove to be key targets for therapeutic intervention.

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Transposons; genomic stability; double-strand breaks; epigenetic reprogramming

Introduction

Transposable elements (TEs) are discrete DNA sequences present in nearly all living organisms, including *Homo sapiens*.[1] These mobile genetic elements possess the remarkable ability to relocate within host genomes. Since the pioneering discovery of genomic instability in maize,[2–4] TEs have been recognized as major genomic constituents, varying substantially in both quantity and quality across species.[5] Whole genome sequencing analysis across mammalian species have revealed TEs comprise large portions of the genome. The proportion of TE-derived sequences varies dramatically: approximately 10% of several fish species, 12% of the *Caenorhabditis elegans*, 37% in mice, and over 80% in some plant species such as maize.[6–8] Although TEs were initially dismissed as "junk" DNA, decades of research have demonstrated that these elements actively shape host genomes co-opt cellular functions to ensure their survival, thereby playing critical roles in generating genomic diversity.[9,10] In-depth exploration of TE functions has led to the development of numerous tools for DNA integration strategies, and powerful genome engineering systems now leverage TEs to manipulate genes both in random or targeted fashions.[11] However, transposition events can have deleterious consequences in vivo, as mobilization of TEs can disrupt normal gene function at target loci and affect neighboring genes. A striking example is the insertional mutagenesis of the tumor suppressor gene adenomatous polyposis coli (APC), where somatic TE insertion into its last exon disrupts gene functionality, and has been linked to colon cancer progression.[12] In addition, transposition events are frequently associated with DSBs that are susceptible to

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