OPEN ACCESS Freely available online

ISSN: 2329-6682
Gene Technology

Perspective

Role of DNA Polymerases in DNA Replication

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DESCRIPTION

Molecular biology and genetics hold that a genome contains the majority of an organism's genetic information. It is made up of DNA oligonucleotides. Protein-coding genes and non-coding genes, as well as other functional regions of the chromosome and any trash DNA, are all included in the nuclear genome. Chloroplasts with a chloroplast genome are found in algae and plants, and mitochondria with a mitochondrial genome are found in practically all eukaryotes. Because just about all eukaryotic animals have nuclear chromosomes as well as additional DNA molecules in the mitochondria, defining eukaryotic genomes is significantly more complex. Most eukaryotes are diploid, which means that each chromosome has two copies in the nucleus, but each chromosome has only one copy in the genome. Because some eukaryotes, such as mammals, have separate sex chromosomes, the technical definition of the genome must include both copies of the sex chromosomes. When referring to the human genome's standard reference genome.

Integrated management of origin activation and polymerases development is required to maintain genome stability. The relationship between these systems and how it affects human genetic illness and cancer is yet unknown. We show that mouse cells with Polymerase instability have decreased genome-wide activation of DNA replication origins, which is independent of origin location. *Trp53* ablation increased Polymerase levels and origin activation while reducing DNA damage in primary Polymerase hypomorphic cells in a transcription-dependent manner. The *TRP53-CDKN1A/P21* axis maintains optimal amounts of replication factors and CDK activity during undisturbed S phase, according to transcriptase study of primary *Trp53* deficient cells. Origin activation is disrupted and genome-wide replication fork advancement is disrupted when this control mechanism is lost. In eukaryotes, DNA replication is carried out by a multiprotein assembly called the replisome, which is activated in a spatiotemporally controlled manner.

The replicative polymerases that create the lagging and leading strands, respectively, are also important components of this machinery. Polymerase, which is essential for GINS loading and the creation of the pre-initiation complex in budding yeast, is also an important part of the CMG. Dysfunctional DNA replication has been linked to a slew of human genetic diseases marked by stunted growth, immunological, and endocrine abnormalities. Furthermore, oncogene-induced disruption of DNA replication, known as replication stress, is thought to be a major contributor to genomic instability in cancer. Oncogene-induced genomic instability in the early stages of tumor genesis is thought to be caused by unregulated control of origin activation in particular. According to Macheret and Halazonetis, activation of oncogenes like CCNE1 (Cyclin E) and MYC leads to the activation of a novel set of replication origins found inside highly transcribed genes, which are generally inhibited by transcription during the G1 phase of the cell cycle. The activation of these ectopic replication origins is triggered by an early G1-S transition produced by oncogene activity, resulting in transcription-replication conflicts and genetic instability. It's unclear whether loss of tumor suppressors like *P53* and *CDKN1A/P21* causes replication stress.

Due to the fact that E2F hyper activation has been linked to replicative stress and DNA damage, the role of *TRP53* and *CDKN1A/P21* in unopposed DNA replication is still debated due to differences in experimental model systems. We previously demonstrated that mice lacking the polymerase 4 subunit of polymerase develop into a complicated developmental disorder marked by diminished growth, morphological abnormalities, and leukopenia, as well as an elevated cancer risk. The loss of polymerase 4 in mouse cells is linked to lower amounts of polymerase, polymerase 1 and polymerase 2 subunits, leading us to believe that polymerase 4 animals are a polymerase hypomorphic mouse model. Nonetheless, we and others have recently demonstrated that polymerase 4 is involved in histone H3-H4 chaperoning at the replication fork; however, the repercussions of losing this activity *in vivo* are unknown. Polymerase 4, along with polymerase 3, is a component of the ATAC acetyl transferase complex, and its absence has recently been linked to increased sensitivity to ATR and PARP inhibitors.

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Received: 06-Jun-2022, Manuscript No. RDT-22-17297; **Editor assigned:** 09-Jun-2022, PreQC No. RDT-22-17297 (PQ); **Reviewed:** 24-Jun-2022, QC No. RDT-22-17297; **Revised:** 01-Jul-2022, Manuscript No. RDT-22-17297 (R); **Published:** 08-Jul-2022, DOI: 10.35248/2329-6682.22.11.194

Citation: King S (2022) Role of DNA Polymerases in DNA Replication. Gene Technol. 11:194.

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While the mechanism behind this event is unknown, understanding it could lead to the discovery of new markers of susceptibility to these substances as well as novel cancer cell weaknesses.

In this study, we show that deletion of polymerase 4 causes lower replication origin activation in primary B cells, regardless of their chromosomal position. Surprisingly, *TRP53* deficiency in animals and cells reverses the phenotypic implications of polymerase instability. While the absence of polymerase 4 causes polymerase to be degraded by the proteasome, the loss of *TRP53* in polymerase hypomorphic cells restores polymerase levels to "near to wild-type" levels due to increased transcription of polymerase subunits. We discovered that genetic deletion of *Trp53* causes suppression of *Cdkn1a/p21* in primary mouse cells, as well as an increase in E2F activity and replication origin activation, in addition to an increase in replication initiation factors, by analyzing the transcriptase and replication dynamics of *Trp53* knockout cells. The CDK inhibitory domain of *CDKN1A/P21* is required for hyper activation of DNA replication origins caused by dysregulation of the *TRP53-CDKN1A/P21* axis, which results in genome-wide perturbation of replication fork progression. This method has far-reaching implications for genomic instability caused by the loss of the tumor suppressors TRP53 and CDKN1A/P21, as well as therapeutic targeted of cancer cells.