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Role of specialized DNA polymerases in the limitation of replicative stress and DNA damage transmission

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ABSTRACT

Replication stress is a strong and early driving force for genomic instability and tumor development. Beside replicative DNA polymerases, an emerging group of specialized DNA polymerases is involved in the technical assistance of the replication machinery in order to prevent replicative stress and its deleterious consequences. During S-phase, altered progression of the replication fork by endogenous or exogenous impediments induces replicative stress, causing cells to reach mitosis with genomic regions not fully duplicated. Recently, specific mechanisms to resolve replication intermediates during mitosis with the aim of limiting DNA damage transmission to daughter cells have been identified. In this review, we detail the two major actions of specialized DNA polymerases that limit DNA damage transmission: the prevention of replicative stress by non-B DNA replication and the recovery of stalled replication forks.

1. Introduction

The replication fork progression is constantly faced with different endogenous or exogenous impediments all along the genome. Exogenous barriers include DNA damage produced by genotoxic components from the environment, radiation, therapeutic treatments and the diet. In contrast, endogenous obstacles come from inherent DNA structures and composition, protein-DNA complexes, modification of the nucleotide pool, the production of oxidative species, transcription-replication machinery collisions, mutations in tumor suppressor genes and oncogenic protein expression [1] . These damaged or difficult-to-replicate DNA regions induce replication fork slowing or stalling, also known as "replicative stress" [2] . Replicative stress is mediated by the uncoupling of helicases from DNA replicative polymerases, generating long stretches of single-stranded DNA (ssDNA) [3] . This situation leads to S-phase checkpoint activation in order to organize replication fork restart but acute replicative stress can also induce collapsed forks and DNA breaks that need dedicated detection, signaling and appropriate DNA repair pathways [4] .
Recently it was shown that mild replicative stress could escape checkpoint detection, leading to the persistence of under-replicated DNA regions or replication intermediates upon mitotic entry. Then, chromosome segregation induce breakage of these unresolved DNA regions that are transmitted to G1 daughter cells, detected by the formation of micronuclei and 53BP1 nuclear bodies [5] . DNA damage transmission caused by replicative stress has been clearly demonstrated at common fragile site loci (CFS) [6,7] . In addition to CFS, it is possible that all genomic regions that are susceptible to be targeted by different sources of replication barriers or prone to form non-B DNA structures become a threat to accurate replication, promoting