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Y-Family DNA Polymerases and Translesion Synthesis

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Abstract

DNA polymerases are specialized in the synthesis and repair of the genetic material. Y-family DNA polymerases lie at the heart of the mutagenesis process, a process commonly known as translesion synthesis. Y-family DNA polymerases have special characteristics of synthesizing the bases on damaged DNA. Translesion synthesis (TLS) is a process carried out by special polymerases for the prevention of cell death. This article mainly emphasizes the process carried out by DNA polymerases for prevention of cell death *viz*., TLS along with their necessities, and also for error-prone replication.

Introduction

DNA polymerases play a vital role in the transmission of genetic information to next generation as they perform the function of DNA synthesis and repair during replication. These are categorized into four families namely A, B, X and Y on the basis of their catalytic subunit. Family A has a role in maturation of Okazaki fragments and DNA repair; family B of DNA polymerases exhibit 3'-5' exonuclease activity; X family has a role in short gaps filling during DNA repair whereas Y family (lesion bypass) has a role in the pathways of DNA lesion tolerance. Y-family DNA polymerases were originally known as UmuC/DinB/Rev1/Rad30 named after each branch of family (Yang, 2014).

Enzymes Included in Y-family DNA polymerases

The Y-family of DNA polymerases include the following enzymes: Prokaryotic DNA polymerase IV (DinB), Prokaryotic DNA repair proteins (UmuC and UmuD), Archaeal DinB homologue DNA polymerase IV, Eukaryotic DNA repair protein (Rev1), Eukaryotic Rad30 homologues DNA polymerase eta and iota, Eukaryotic DinB homologue DNA polymerase kappa.

Requirement of DNA Polymerases in Bypass

Lesions in DNA base causes chemical and structural changes at the damage site which causes distortion and instability of the double helix. In order to bypass a lesion, two different polymerases are suggested in translesion DNA synthesis. First polymerase fit in with the damaged base which directly incorporates the nucleotide opposite to the lesion; second polymerase help in the extension of DNA primer beyond the DNA lesion for various base pairs until the damaged DNA safely handled by replicase.

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Characteristic Features

These polymerases have a unique and specific feature that differentiates it from other family DNA polymerases. They have low catalytic efficiency; a low fidelity of synthesis on intact DNA; a low processivity as compare to DNA replicases; absence of exonuclease activity and proofreading ability; have a domain, called PAD (polymerase-associated domain) also referred to as wrist or little fingers domain; unpacked DNA binding pocket for the nascent base pair that allows the enzymes to accommodate deformed DNA in the active site as a result of which the enzymes polymerize on damaged DNA. The features such as low catalytic efficiency and low processivity ensure that they do not hold on a replication fork for numerous base pairs and engage only when necessary.

Role of Y Family DNA Polymerases

Y family DNA polymerases have a unique function in translesion synthesis (TLS) that passes the damaged bases for the normal progress of replication fork. When the cell fails to overcome the DNA lesion, then these lesions are passed by the family Y polymerases resulting in the translesion synthesis. They have a role in the first step of translesion synthesis while the second step has been shown to perform by the B family polymerases (Jarosz *et al.,* 2007). One homologue was also found in the *Arabidopsis*, but remains to be characterized functionally.

Y family DNA polymerases also have a 'non-canonical' role, in addition to their role in damaged DNA replication. They have a role in excision repair processes such as NER (Nucleotide excision repair), BER (Base excision repair) etc. Pol η has a role in some forms of homologous recombination.

Necessity of TLS

TLS DNA polymerases have a significant role in preventing cell death at the cost of increasing the rate of mutations. Being an efficient process, it is more advantageous than other mechanisms because interruption in the DNA synthesis for a long time causes double-strand break (DSB) in the DNA that would produce genomic rearrangements. Furthermore, the consequences of TLS may be non-significant as it is error-free in many instances. In mammals, the majority of the genome is non-coding ensuring no adverse effects of mutation on cellular physiology.

Mechanism of TLS

TLS is a multistep process. Firstly, replicative DNA polymerase halts at the DNA damage site and then replaced by a TLS polymerase. After that, TLS polymerase inserts a correct or incorrect base opposite to the damaged DNA and extended subsequently to complete the translesion synthesis. All the TLS polymerases are separated from the strand after the synthesis of a short segment of damaged DNA which are then suddenly replaced by the replicative polymerase for the normal synthesis (Sakamoto, 2019). The mechanism of TLS has shown in Figure 1.

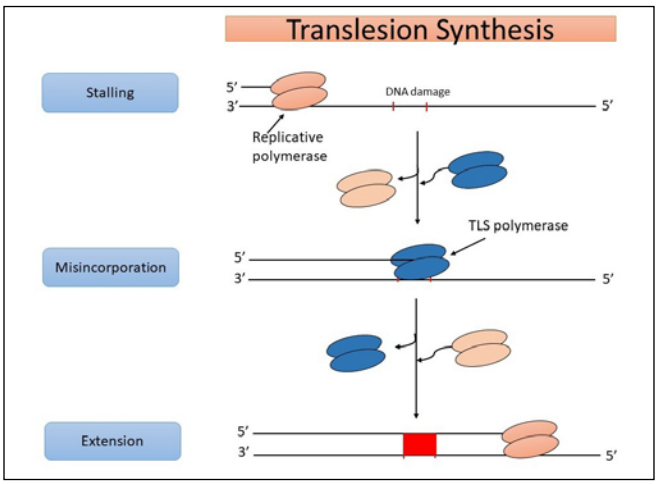

Figure 1: Mechanism of Translesion synthesis

In vertebrates, four Y family polymerases are there, namely Pol I, Pol η, Rev 1, and Pol κ possessing lesion bypass capacity for the particular lesion. Pol η has shown high efficiency in bypassing of T-T dimer but show low efficiency in bypassing lesion with pol I. In eukaryotes, Pol η has been shown to perform translesion synthesis. In plants, Pol ζ, Pol η and REV 1 are the TLS polymerases which are involved in an error-prone bypass mechanism (Jarosz et al., 2007).

Occurrence of TLS

TLS occurs in the G2 phase of the cell as the Pol η, Rev 3, or Rad 18 are induced only in the G2 phase but the occurrence of TLS in the S phase of replication has also been seen. Rev 1 is involved in assisting the TLS at the replication fork, while ubiquitylation of PCNA (Proliferating cell nuclear antigen) is needed behind the replication fork. TLS in human and mouse cells is higher in G2 phase as compared to S phase indicating the lags of TLS behind the chromosomal replication. Plant genome encompasses a lesser number of TLS polymerases as compared to the human genome.

Role of Lesion Itself

It remains still unclear what decides the selection of polymerase at specific lesion sites. Based on the mechanism of action of TLS, it seems likely that the lesion itself plays an important role in deciding which polymerase is eventually employed in replication. It may also be that the condition in which the lesion is found, restrict options for its bypass.

Conclusion

Our knowledge regarding the role of Y-family polymerases has increased significantly in recent past years. Y-family polymerases are the reasons for

the mutagenic events, having a crucial role in carcinogenesis. Specialized TLS polymerases may be useful aims for anticancer drugs. Plants, like other eukaryotes, can possess a broad reservoir of TLS polymerases but this was not investigated systematically. The open question is still not resolved why they are not thoroughly illuminated in the plant? Hence, they provide a potential platform to the researcher to uproot the integration of TLS in the molecular world. For better understanding of the biological responses, we need to investigate the mechanisms that join the Y-family members into several elements of the DNA damage response.

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