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Eukaryotic DNA polymerase (4)

Eukaryotic cells harbour several types of DNA polymerases, distributed across the nucleus and organelles like mitochondria and chloroplasts. In the nucleus, three main types of DNA polymerases are involved in DNA replication DNA Pol α, DNA Pol δ, and DNA Pol ε.

DNA Pol α: DNA polymerase α (alpha) is unique for its dual activity as both a DNA polymerase and a primase, responsible for synthesizing short RNA primers complementary to a single-stranded DNA template. These primers, called initiator RNA (iRNA), are then extended by Pol α into initiator DNA (iDNA). However, Pol α lacks proofreading activity and shows low processivity. After initiating DNA synthesis, Pol α is replaced by either Pol δ or Pol ε, which carry out elongation.

DNA poly δ: DNA polymerase delta (Pol δ) is an enzyme complex in eukaryotes that plays a key role in DNA replication, repair, and recombination. It is one of three polymerases that replicate bulk DNA in eukaryotic cells, along with primase DNA polymerase α (Pol α) and DNA polymerase ε (Pol ε). Pol δ is the primary replicase for the lagging strand and has 5′→3′ DNA-directed polymerase activity and 3′→5′ exonuclease activity. Pol δ is a multi-subunit enzyme made up of 4 subunits named POL A-D. It exhibits increased processivity when interacting with the proliferating cell nuclear antigen (PCNA). Also, the multisubunit protein replication factor C, through its role as the clamp loader for PCNA (which involves catalysing the loading of PCNA on to DNA) is important for DNA Pol δ function.

DNA Pol ε: DNA polymerase epsilon is a member of the DNA polymerase family of enzymes found in eukaryotes. It is composed of the four subunits namely, POLE (central catalytic unit), and POLE 2-4. Either DNA polymerase epsilon or DNA polymerase delta along with DNA ligase can be used to repair UV-damaged DNA. DNA polymerase epsilon proves to be best suited for nucleotide excision repair. DNA polymerase epsilon is independent of both PCNA and RFC, and produces mostly ligated DNA products. However, under one condition i.e. nucleotide excision repair, it requires PCNA (proliferating cell nuclear antigen), RFC (replication factor C) and RPA (replication protein A).

In addition to three primary nuclear polymerases there are several other DNA polymerases. DNA Pol γ functions as the primary polymerase for mitochondrial DNA replication. It is interesting to note that inhibitors like aphidicolin selectively target nuclear DNA polymerases without affecting Pol γ. Family X polymerases, including pol β, σ, λ, μ, and TdT, are predominantly found in vertebrates and are essential for various repair mechanisms. Pol β, for instance, facilitates short-patch base excision repair, while Pol λ and Pol μ play roles in non-homologous end-joining, aiding in the rejoining of DNA double-strand breaks. Additionally, telomerase, a ribonucleoprotein, extends the ends of linear chromosomes, compensating for the

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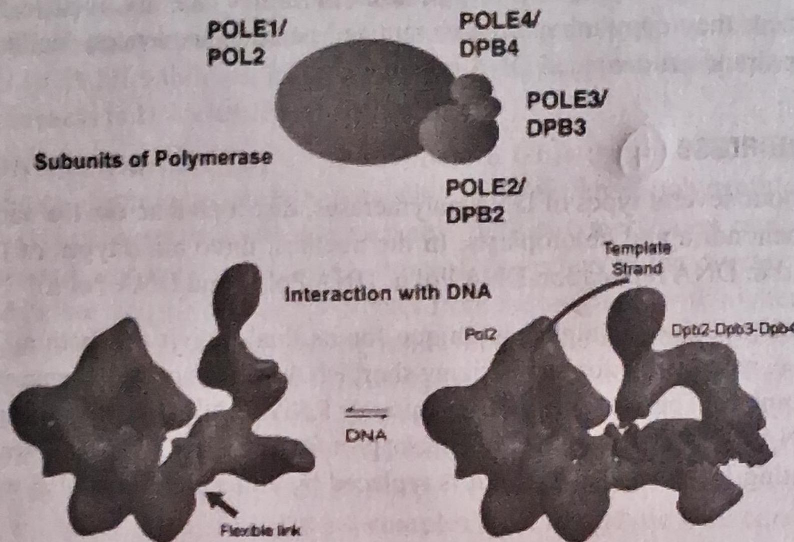

Fig. 2.5. Structure of the eukaryotic DNA polymerase epsilon (After Pursell and Kunkel).

2.3 THETA MODEL FOR CIRCULAR DNA REPLICATION

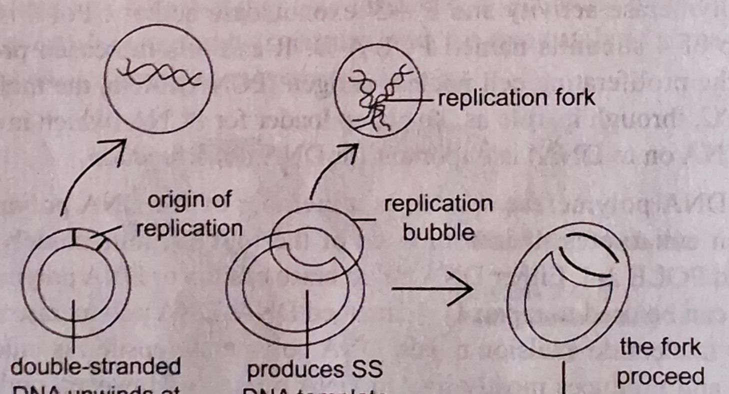

Fig. 2.6. Theta model of circular DNA replication.

(i) Initiation- In ds circular DNA of bacteria begins at a conserved sequence region called as the origin of replication or ORI C. At this region different initiation factor or proteins started to assemble. These initiator proteins regulate that replication occurs only once every cell cycle. These dsDNA unwinds at the origin of replication.

(ii) Elongation- At the ori site dsDNA started producing single stranded templates for the synthesis of new DNA. A replication bubble forms usually with a replication fork at each end whereas proteins at ori C began to travel in opposite direction and referred as bidirectional replication. This elongation process is brought about by a complex of protein called **replisome**. Replisome moves along DNA and the parental strands started to unwind and used as a template on which daughter strands are synthesized.

(iii) Termination- On circular chromosomes, opposite the ori C is the terminus region which consists of several 'Ter' sites. This is the site where terminator proteins are present which halts the two replication forks producing two circular DNA molecules.