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**DEPARTMENT: PHYSIOLOGY**

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* HIGHLIGHT THE STEPS OF DNA REPLICATION
* OUTLINE THE FUNCTIONS OF DNA REPLICATION ENZYMES.

**ASSIGNMENT**

Replication involves the production of identical helices of DNA from one double stranded molecule of DNA

**STEPS OF DNA REPLICATION**

Steps of DNA can be thought of in three stages; **Initiation, Elongation, Termination**

**INITIATION OR REPLICATION FORK FORMATION**: Before DNA can be replicated, the double stranded molecule must be “unzipped” into two single strands. DNA has four bases called adenine (A), thymine (T), cytosine (C) and guanine (G) that form pairs between the two strands. Adenine only pairs with thymine and cytosine only binds with guanine. In order to unwind DNA, these interactions between base pairs must be broken. This is performed by an enzyme known as DNA helicase. DNA helicase disrupts the hydrogen bonding between base pairs to separate the strands into a Y shape known as the replication fork. This area will be the template for replication to begin.

DNA is directional in both strands, signified by a 5' and 3' end. This notation signifies which side group is attached the DNA backbone. The 5' end has a phosphate (P) group attached, while the 3' end has a hydroxyl (OH) group attached. This directionality is important for replication as it only progresses in the 5' to 3' direction. However, the replication fork is bi-directional; one strand is oriented in the 3' to 5' direction (leading strand) while the other is oriented 5' to 3' (lagging strand). The two sides are therefore replicated with two different processes to accommodate the directional difference. DNA Primase is another enzyme that is important in DNA replication. It synthesises a small RNA primer, which acts as a ‘kick-starter’ for DNA Polymerase. DNA Polymerase is the enzyme that is ultimately responsible for the creation and expansion of the new strands of DNA.

**ELONGATION:** The leading strand is the simplest to replicate. Once the DNA strands have been separated, a short piece of RNA called a primer binds to the 3' end of the strand. One of the templates is read in a 3’ to 5’ direction, which means that the new strand will be formed in a 5’ to 3’ direction (as the two strands are antiparallel to each other). This newly formed strand is referred to as the Leading Strand. Along this strand, DNA Primase only needs to synthesise an RNA primer once, at the beginning, to help initiate DNA polymerase to continue extending the new DNA strand. This is because DNA Polymerase is able to extend the new DNA strand normally, by adding new nucleotides to the 3’ end of the new strand (how DNA Polymerase usually works).

However, the other template strand is antiparallel, and is therefore read in a 5’ to 3’ direction, meaning the new DNA strand being formed will run in a 3’ to 5’ direction. This is an issue as DNA Polymerase doesn’t extend in this direction. To counteract this, DNA Primase synthesises a new RNA primer approximately every 200 nucleotides, to prime DNA synthesis to continue extending from the 5’ end of the new strand. To allow for the continued creation of RNA primers, the new synthesis is delayed and is such called the Lagging Strand.

The leading strand is one complete strand, while the lagging strand is not. It is instead made out of multiple ‘mini-strands’, known of Okazaki fragments. These fragments occur due to the fact that new primers have to be synthesised, therefore causing multiple strands to be created, as opposed to the one initial primer that is used with the leading strand.

**TERMINATION**: The process of expanding the new DNA strands continues until there is either no more DNA template left to replicate (i.e. at the end of the chromosome), or two replication forks meet and subsequently terminate. Once both the continuous and discontinuous strands are formed, an enzyme called exonuclease removes all RNA primers from the original strands. These primers are then replaced with appropriate bases. Another exonuclease “proofreads” the newly formed DNA to check, remove and replace any errors. Another enzyme called DNA ligase joins Okazaki fragments together forming a single unified strand. The ends of the linear DNA present a problem as DNA polymerase can only add nucleotides in the 5′ to 3′ direction. The ends of the parent strands consist of repeated DNA sequences called telomeres. Telomeres act as protective caps at the end of chromosomes to prevent nearby chromosomes from fusing. A special type of DNA polymerase enzyme called telomerase catalyzes the synthesis of telomere sequences at the ends of the DNA. Once completed, the parent strand and its complementary DNA strand coils into the familiar double helix shape. In the end, replication produces two DNA molecules, each with one strand from the parent molecule and one new strand.

**DNA REPLICATION ENZYMES**

DNA replication would not occur without enzymes that catalyze various steps in the process. Enzymes that participate in the eukaryotic DNA replication process include:

**FUNCTIONS**

* **DNA helicase** - unwinds and separates double stranded DNA as it moves along the DNA. It forms the replication fork by breaking hydrogen bonds between nucleotide pairs in DNA.
* **DNA primase** - a type of RNA polymerase that generates RNA primers. Primers are short RNA molecules that act as templates for the starting point of DNA replication.
* **DNA polymerases** - synthesize new DNA molecules by adding nucleotides to leading and lagging DNA strands.
* **Topoisomerase or DNA Gyrase** - unwinds and rewinds DNA strands to prevent the DNA from becoming tangled or supercoiled.
* **Exonucleases** - group of enzymes that remove nucleotide bases from the end of a DNA chain.
* **DNA ligase** - joins DNA fragments together by forming phosphodiester bonds between nucleotides.