LECTURE 2
(Chapter 11)
DNA Replication
Slides 1-30; 41-56; 58-66

On your own:
Slides 31-40; 57
INTRODUCTION

• DNA replication is the process by which the genetic material is copied
  – The original DNA strands are used as templates for the synthesis of new strands

• It occurs very quickly, very accurately and at the appropriate time in the life of the cell
  – This chapter examines how!
11.1 STRUCTURAL OVERVIEW OF DNA REPLICATION

- DNA replication relies on the complementarity of DNA strands
  - The AT/GC rule or Chargaff’s rule

- The process can be summarized as such
  - The two complementary DNA strands come apart
  - Each serves as a template strand for the synthesis of new complementary DNA strands
  - The two newly-made DNA strands = daughter strands
  - The two original DNA strands = parental strands
A pairs with T and G pairs with C during synthesis of a new strand.

**Figure 11.1**

(a) The mechanism of DNA replication

(b) The products of replication
Experiment 11A: Which Model of DNA Replication is Correct?

- In the late 1950s, three different mechanisms were proposed for the replication of DNA
  - **Conservative model**
    - Both parental strands stay together after DNA replication
  - **Semiconservative model**
    - The double-stranded DNA contains one parental and one daughter strand following replication
  - **Dispersive model**
    - Parental and daughter DNA are interspersed in both strands following replication
Figure 11.2

(a) Conservative model

(b) Semiconservative model

(c) Dispersive model

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In 1958, Matthew Meselson and Franklin Stahl devised a method to investigate these models:
- They found a way to experimentally distinguish between daughter and parental strands.

Their experiment can be summarized as such:
- Grow *E. coli* in the presence of $^{15}$N (a heavy isotope of Nitrogen) for many generations.
  - The population of cells had heavy-labeled DNA.
- Switch *E. coli* to medium containing only $^{14}$N (a light isotope of Nitrogen).
- Collect sample of cells after various times.
- Analyze the density of the DNA by centrifugation using a CsCl gradient.
The Hypothesis

– Based on Watson’s and Crick’s ideas, the hypothesis was that DNA replication is semiconservative.

Testing the Hypothesis

■ Refer to Figure 11.3
1. Add an excess of $^{14}$N-containing compounds to the bacterial cells so all of the newly made DNA will contain $^{14}$N.

2. Incubate the cells for various lengths of time. Note: The $^{15}$N-labeled DNA is shown in purple and the $^{14}$N-labeled DNA is shown in blue.

3. Lyse the cells by the addition of lysozyme and detergent, which disrupt the bacterial cell wall and cell membrane, respectively.

4. Load a sample of the lysate onto a CsCl gradient containing ethidium bromide. (Note: The average density of DNA is around 1.7 g/cm$^3$, which is well isolated from other cellular macromolecules.)

5. Centrifuge the gradients until the DNA molecules reach their equilibrium densities.

6. DNA within the gradient can be observed under a UV light.

(Result shown here is after 2 generations.)
The Data

Generations After $^{14}$N Addition

Interpreting the Data

After ~ two generations, DNA is of two types: “light” and “half-heavy”.
This is consistent with only the semi-conservative model.

After one generation, DNA is “half-heavy”.
This is consistent with both semi-conservative and dispersive models.

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11.2 BACTERIAL DNA REPLICATION

- Figure 11.4 presents an overview of the process of bacterial chromosomal replication
  - DNA synthesis begins at a site termed the origin of replication
    - Each bacterial chromosome has only one origin of replication
  - Synthesis of DNA proceeds bidirectionally around the bacterial chromosome
  - The two replication forks eventually meet at the opposite side of the bacterial chromosome
    - This ends replication
Figure 11.4

(a) Bacterial chromosome replication

(b) Autoradiograph of an *E. coli* chromosome in the act of replication
Initiation of Replication

- The origin of replication in *E. coli* is termed *oriC*
  - origin of Chromosomal replication

- Three types of DNA sequences in *oriC* are functionally significant
  - AT-rich region
  - DnaA boxes
  - GATC methylation sites

- Refer to Figure 11.5
Figure 11.5

E. coli chromosome

AT-rich region

5′–GGATCCTGGGTTTATTTAGAGATCTTCTGTTCTATCTAGGGACCATATAATTCTCTAGATAAAATTTACTGTCATCTAGACAGAGATA

DnaA box

TGATCTCTTTATTAGGATCGACTGCCCCTGTGAATAACAGGATCGGCTACACTAGAGAAATATCGGTGATTTATAGTAATACCTAGAAGACCTA

DnaA box

TTAAGATCAACACCTGGAAAAGGATCATTAACTGTGAATGACTGCTGATCAAATTCTATGTGGGACCTTTCTAGAAATTGAGGACTACAATAGCCTATA

DnaA box

CCTGGACCGTATAAGCTGGGATCAAGATGAGGGTTATTACACAGCTCAAAAAAGACCTGGGCAATTGACCCCATTGATGTGTCGAGTTTT

DnaA box

ACTGAAACAGTGTTCTCTTGAGTAACCTACCGGTGTGACCTACCCCTTCATTTGATGGCCAACTAGTTGTCAGAG

DnaA box

GACAGATTATCCACAGTAGATCGC–3′

CTGTCTCAATAGGTGTCACTCTAGCG
Next, DNA helicases bind
Figure 11.6

Composed of six subunits
Travels along the DNA in the 5’ to 3’ direction
Uses energy from ATP

Helicase

DNA helicase separates the DNA in both directions, creating 2 replication forks.

Bidirectional replication is initiated
DNA helicase separates the two DNA strands by breaking the hydrogen bonds between them.

This generates positive supercoiling ahead of each replication fork.

- **DNA gyrase** travels ahead of the helicase and alleviates these supercoils.

Single-strand binding proteins bind to the separated DNA strands to keep them apart.

Then short (10 to 12 nucleotides) RNA primers are synthesized by DNA primase.

- These short RNA strands start, or “prime”, DNA synthesis.
  - The leading strand has a single primer, the lagging strand needs multiple primers.
  - They are eventually removed and replaced with DNA.
Functions of key proteins involved with DNA replication

- DNA helicase breaks the hydrogen bonds between the DNA strands.
- Topoisomerase alleviates positive supercoiling.
- Single-strand binding proteins keep the parental strands apart.
- Primase synthesizes an RNA primer.
- DNA polymerase III synthesizes a daughter strand of DNA.
- DNA polymerase I excises the RNA primers and fills in with DNA (not shown).
- DNA ligase covalently links the Okazaki fragments together.

Figure 11.7
<table>
<thead>
<tr>
<th>Common Name</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>DnaA protein</td>
<td>Binds to DnaA boxes within the origin to initiate DNA replication</td>
</tr>
<tr>
<td>DnaC protein</td>
<td>Aids DnaA in the recruitment of DNA helicase to the origin</td>
</tr>
<tr>
<td>DNA helicase (DnaB)</td>
<td>Separates double-stranded DNA</td>
</tr>
<tr>
<td>Topoisomerase</td>
<td>Removes positive supercoiling ahead of the replication fork</td>
</tr>
<tr>
<td>Single-strand binding protein</td>
<td>Binds to single-stranded DNA and prevents it from re-forming a double-stranded structure</td>
</tr>
<tr>
<td>Primase</td>
<td>Synthesizes short RNA primers</td>
</tr>
<tr>
<td>DNA polymerase III</td>
<td>Synthesizes DNA in the leading and lagging strands</td>
</tr>
<tr>
<td>DNA polymerase I</td>
<td>Removes RNA primers, fills in gaps with DNA</td>
</tr>
<tr>
<td>DNA ligase</td>
<td>Covalently attaches adjacent Okazaki fragments</td>
</tr>
<tr>
<td>Tus</td>
<td>Binds to ter sequences and prevents the advancement of the replication fork</td>
</tr>
</tbody>
</table>
DNA Polymerases

- DNA polymerases are the enzymes that catalyze the attachment of nucleotides to synthesize a new DNA strand

- In *E. coli* there are five proteins with polymerase activity
  - DNA pol I, II, III, IV and V
  - DNA pol I and III
    - Normal replication
  - DNA pol II, IV and V
    - DNA repair and replication of damaged DNA
DNA Polymerases

- **DNA pol I**
  - Composed of a single polypeptide
  - Removes the RNA primers and replaces them with DNA

- **DNA pol III**
  - Responsible for most of the DNA replication
  - Composed of 10 different subunits
    - The $\alpha$ subunit catalyzes bond formation between adjacent nucleotides (DNA synthesis)
    - The other 9 fulfill other functions
  - The complex of all 10 subunits is referred to as the DNA pol III holoenzyme
Bacterial DNA polymerases may vary in their subunit composition

However, they all have the same type of catalytic subunit

Figure 11.8

(a) Schematic side view of DNA polymerase III
**Figure 11.9** Unusual features of DNA polymerase function

- **DNA polymerases cannot initiate DNA synthesis**
  - Problem is overcome by the RNA primers synthesized by primase

- **DNA polymerases can attach nucleotides only in the 5’ to 3’ direction**
  - Problem is overcome by synthesizing the new strands both toward, and away from, the replication fork
The two new daughter strands are synthesized in different ways

- **Leading strand**
  - One RNA primer is made at the origin
  - DNA pol III attaches nucleotides in a 5’ to 3’ direction as it slides toward the opening of the replication fork

- **Lagging strand**
  - Synthesis is also in the 5’ to 3’ direction
    - However it occurs away from the replication fork
  - Many RNA primers are required
  - DNA pol III uses the RNA primers to synthesize small DNA fragments (1000 to 2000 nucleotides each)
    - These are termed **Okazaki fragments** after their discoverers
- **DNA pol I** removes the RNA primers and fills the resulting gap with DNA
  - It uses a 5’ to 3’ exonuclease activity to digest the RNA and 5’ to 3’ polymerase activity to replace it with DNA

- After the gap is filled a covalent bond is still missing

- **DNA ligase** catalyzes the formation of a phosphodiester bond
  - Thereby connecting the DNA fragments
Figure 11.10

DNA strands separate at origin, creating 2 replication forks.

Primers are needed to initiate DNA synthesis. The synthesis of the leading strand occurs in the same direction as the movement of the replication fork. The first Okazaki fragment of the lagging strand is made in the opposite direction.

The leading strand elongates, and a second Okazaki fragment is made.

The leading strand continues to elongate. A third Okazaki fragment is made, and the first and second are connected together.

First and second Okazaki fragments have been connected to each other.

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The synthesis of leading and lagging strands from a single origin of replication

Figure 11.11
The Reaction of DNA Polymerase

- DNA polymerases catalyzes the formation of a covalent (ester) bond between the
  - Innermost phosphate group of the incoming deoxyribonucleoside triphosphate
  - AND
  - 3’-OH of the sugar of the previous deoxynucleotide
- In the process, the last two phosphates of the incoming nucleotide are released
  - In the form of pyrophosphate (PPᵢ)
  - Refer to figure 11.12
Figure 11.12

New DNA strand

5′ end

Cytosine :: Guanine

Guanine :: Cytosine

Thymine :: Adenine

3′ end

New ester bond

Pyrophosphate (PPI)

Innermost phosphate

Original DNA strand

5′ end

3′ end

5′ end

3′ end
DNA Polymerase III is a Processive Enzyme

- DNA polymerase III remains attached to the template as it is synthesizing the daughter strand

- This **processive** feature is due to several different subunits in the DNA pol III holoenzyme
  - $\beta$ subunit forms a dimer in the shape of a ring around template DNA
    - It is termed the clamp protein
    - Once bound, the $\beta$ subunits can freely slide along dsDNA
    - Promotes association of holoenzyme with DNA
  - $\gamma$ complex catalyzes $\beta$ dimer clamping to the DNA
    - It is termed the clamp-loader complex
    - Includes $\gamma$, $\delta$, $\delta'$, $\chi$ and $\psi$ subunits
DNA Polymerase III is a Processive Enzyme

- The effect of processivity is quite remarkable
  - In the absence of the β subunit
    - DNA pol III falls off the DNA template after about 10 nucleotides have been polymerized
    - Its rate is ~ 20 nucleotides per second
  - In the presence of the β subunit
    - DNA pol III stays on the DNA template long enough to polymerize up to 500,000 nucleotides
    - Its rate is ~ 750 nucleotides per second
Termination of Replication

- On the opposite side of the chromosome to oriC is a pair of termination sequences called ter sequences
  - These are designated T1 and T2
    - T1 stops counterclockwise forks, T2 stops clockwise forks

- The protein tus (termination utilization substance) binds to the ter sequences
  - tus bound to the ter sequences stops the movement of the replication forks

- Refer to Figure 11.13
Figure 11.13

Prevents advancement of fork moving left-to-right (clockwise fork)

Prevents advancement of fork moving right-to-left (counterclockwise fork)
Termination of Replication

- DNA replication ends when oppositely advancing forks meet (usually at $T1$ or $T2$)
- Finally DNA ligase covalently links the two daughter strands
- DNA replication often results in two intertwined molecules
  - Intertwined circular molecules are termed catenanes
  - These are separated by the action of topoisomerase
Figure 11.14

Catenanes

Replication

Decatenation via topoisomerase

Catalyzed by DNA topoisomerase
Proofreading Mechanisms

- DNA replication exhibits a high degree of **fidelity**
  - Mistakes during the process are extremely rare
    - DNA pol III makes only one mistake per $10^8$ bases made

- There are several reasons why fidelity is high
  1. Instability of mismatched pairs
  2. Configuration of the DNA polymerase active site
  3. Proofreading function of DNA polymerase
Proofreading Mechanisms

1. Instability of mismatched pairs
   - Complementary base pairs have much higher stability than mismatched pairs
   - Stability of base pairs only accounts for part of the fidelity
     - Error rate for mismatched base pairs is 1 per 1,000 nucleotides

2. Configuration of the DNA polymerase active site
   - DNA polymerase is unlikely to catalyze bond formation between mismatched pairs
   - This induced-fit phenomenon decreases the error rate to a range of 1 in 100,000 to 1 million
3. Proofreading function of DNA polymerase

- DNA polymerases can identify a mismatched nucleotide and remove it from the daughter strand.

- The enzyme uses a 3’ to 5’ exonuclease activity to digest the newly made strand until the mismatched nucleotide is removed.

- DNA synthesis then resumes in the 5’ to 3’ direction.
  - Refer to figure 11.16.
Mismatch causes DNA polymerase to pause, leaving mismatched nucleotide near the 3′ end.

The 3′ end enters the exonuclease site.

At the 3′ exonuclease site, the strand is digested in the 3′ to 5′ direction until the incorrect nucleotide is removed.

Site where DNA backbone is cut

Figure 11.16  A schematic drawing of proofreading
Experiment 11B: DNA Replication Can Be Studied In Vitro

• The *in vitro* study of DNA replication was pioneered by Arthur Kornberg in the 1950s
  – He received a Nobel Prize for his efforts in 1959

• Kornberg hypothesized that deoxyribonucleoside triphosphates are the precursors of DNA synthesis

• He also knew that long DNA strands can be precipitated in an acidic solution while free nucleotides cannot
Experiment 11B: DNA Replication Can Be Studied In Vitro

• In this experiment, Kornberg mixed the following
  – An extract of proteins from *E. coli*
  – Template DNA
  – Radiolabeled nucleotides

• These were incubated for sufficient time to allow the synthesis of new DNA strands
  – Addition of acid will precipitate these DNA strands
  – Centrifugation will separate them from the radioactive nucleotides leftover in the supernatant (unincorporated)
The Hypothesis

– DNA synthesis can occur in vitro if all the necessary components are present

Testing the Hypothesis

- Refer to Figure 11.19
1. Mix together the extract of *E. coli* proteins, template DNA that is not radiolabeled, and δ³²P-radiolabeled deoxyribonucleoside triphosphates. This is expected to be a complete system that contains everything necessary for DNA synthesis. As a control, a second sample is made in which the template DNA was omitted from the mixture.

2. Incubate the mixture for 30 minutes at 37°C.

3. Add perchloric acid to precipitate DNA. (It does not precipitate free nucleotides.)

4. Centrifuge the tube. Note: The radiolabeled deoxyribonucleoside triphosphates that have not been incorporated into DNA will remain in the supernatant.

5. Collect the pellet, which contains precipitated DNA and proteins. (The control pellet is not expected to contain DNA.)

6. Count the amount of radioactivity in the pellet using a scintillation counter. (See the Appendix.)
# The Data

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Amount of Radiolabeled DNA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete system</td>
<td>3,300</td>
</tr>
<tr>
<td>Control (template DNA omitted)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Calculated in picomoles of $^{32}$P-labeled DNA.
Interpreting the Data

- Taken together, these results indicate that this technique can be used to measure the synthesis of DNA *in vitro*

E. coli proteins + nonlabeled template DNA + radiolabeled nucleotides

= Radiolabeled product

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<tr>
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<td>0</td>
</tr>
</tbody>
</table>

*Calculated in picomoles of ³²P-labeled DNA.

Expected result because the template is necessary for replication
11.3 EUKARYOTIC DNA REPLICATION

• Eukaryotic DNA replication is not as well understood as bacterial replication
  – The two processes do have extensive similarities,
    • The types of bacterial enzymes described in Table 11.1 have also been found in eukaryotes
  – Nevertheless, DNA replication in eukaryotes is more complex
    • Large linear chromosomes
    • Chromatin is tightly packed within nucleosomes
    • More complicated cell cycle regulation
Multiple Origins of Replication

- Eukaryotes have long linear chromosomes
  - They therefore require multiple origins of replication
    - To ensure that the DNA can be replicated in a reasonable amount of time

- In 1968, Huberman and Riggs provided evidence for multiple origins of replication
  - Refer to Figure 11.21

- DNA replication proceeds bidirectionally from many origins of replication
  - Refer to Figure 11.22
Figure 11.21
Figure 11.22

Before S phase

During S phase

End of S phase
Eukaryotes Contain Several Different DNA Polymerases

- Mammalian cells contain well over a dozen different DNA polymerases
  - Refer to Table 11.4

- Four: alpha (\(\alpha\)), delta (\(\delta\)), epsilon (\(\varepsilon\)) and gamma (\(\gamma\)) have the primary function of replicating DNA
  - \(\alpha\), \(\delta\) and \(\varepsilon\) → Nuclear DNA
  - \(\gamma\) → Mitochondrial DNA
Telomeres and DNA Replication

- Linear eukaryotic chromosomes have telomeres at both ends

- The term telomere refers to the complex of telomeric DNA sequences and bound proteins
Telomeric sequences consist of
- Moderately repetitive tandem arrays
- 3’ overhang that is 12-16 nucleotides long

Figure 11.24

Telomeric sequences typically consist of
- Several guanine nucleotides
- Many thymine nucleotides

Refer to Table 11.5
<table>
<thead>
<tr>
<th>Group</th>
<th>Examples</th>
<th>Telomeric Repeat Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammals</td>
<td>Humans</td>
<td>TTAGGG</td>
</tr>
<tr>
<td>Slime molds</td>
<td><em>Physarum, Didymium</em></td>
<td>TTAGGG</td>
</tr>
<tr>
<td></td>
<td><em>Dictyostelium</em></td>
<td>AG_(1−8)</td>
</tr>
<tr>
<td>Filamentous fungi</td>
<td><em>Neurospora</em></td>
<td>TTAGGG</td>
</tr>
<tr>
<td>Budding yeast</td>
<td><em>Saccharomyces cerevisiae</em></td>
<td>TG_(1−3)</td>
</tr>
<tr>
<td>Ciliates</td>
<td><em>Tetrahymena</em></td>
<td>TTGGGG</td>
</tr>
<tr>
<td></td>
<td><em>Paramecium</em></td>
<td>TTGGG(T/G)</td>
</tr>
<tr>
<td></td>
<td><em>Euplotes</em></td>
<td>TTTTGGGG</td>
</tr>
<tr>
<td>Higher plants</td>
<td><em>Arabidopsis</em></td>
<td>TTTAGGG</td>
</tr>
</tbody>
</table>
DNA polymerases possess two unusual features:

1. They synthesize DNA only in the 5’ to 3’ direction.
2. They cannot initiate DNA synthesis.

These two features pose a problem at the 3’ ends of linear chromosomes—the end of the strand cannot be replicated!

**Figure 11.25**

DNA polymerase cannot link these two nucleotides together without a primer.

No place for a primer.

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Therefore if this problem is not solved
  - The linear chromosome becomes progressively shorter with each round of DNA replication

Indeed, the cell solves this problem by adding DNA sequences to the ends of telomeres

This requires a specialized mechanism catalyzed by the enzyme telomerase

Telomerase contains protein and RNA
  - The RNA is complementary to the DNA sequence found in the telomeric repeat
    - This allows the telomerase to bind to the 3’ overhang
The binding-polymerization-translocation cycle can occur many times. This greatly lengthens one of the strands.

**Figure 11.26**

**Step 1 = Binding**
- Telomerase reverse transcriptase (TERT) activity
- The binding-polymerization-translocation cycle can occur many times
- This greatly lengthens one of the strands

**Step 2 = Polymerization**
- Telomerase synthesizes a 6-nucleotide repeat.
- Telomerase moves 6 nucleotides to the right and begins to make another repeat.
- The complementary strand is made by primase, DNA polymerase, and ligase.

**Step 3 = Translocation**
- The end is now lengthened
- RNA primer

Telomerase synthesizes a 6-nucleotide repeat. Telomerase moves 6 nucleotides to the right and begins to make another repeat. The complementary strand is made by primase, DNA polymerase, and ligase. The end is now lengthened.
Polymerase Chain Reaction
• Polymerase Chain Reaction (PCR)
  – 1983, Kary Mullis
• Copies (“amplifies”) DNA in a test tube using the same type of chemistry that cells use to copy DNA
  – Exponential amplification of specific, short (usually 2,000 bp or less) sequences of DNA
  – Products are called amplicons
• Highly sensitive
• Can amplify small quantities
• Rapid and robust
• **Reaction ingredients:**
  – PCR Primers
    • Short, single-stranded DNA polynucleotides that are complementary to the sequences which **flank** the target region
    • Made on DNA synthesizer
  – dNTPs (in abundance)
  – Template DNA
  – DNA Polymerase
    • Thermostable (e.g. Taq polymerase)
  – MgCl$_2$ and buffer
• PCR steps:
  – Denaturation (94 deg C)
  – Annealing (typically 50-60 deg C)
    • Set just below melting temperature of primers
    • 4 + 2 rule
  – Extension (72 deg C)
    • Optimum temp for taq polymerase
  – Cycling (denaturation, annealing, extension)
    • Typically 20-30 times
Figure 18.5

(a) The outcome of a PCR experiment

Many copies of the gene of interest, flanked by the regions where the primers bind.

(b) The 3 steps of a PCR cycle

Primer binding near one end of the gene

A different primer binding near the other end of the gene

Chromosomal DNA

Many PCR cycles
- PCR is carried out in a **thermocycler**, which automates the timing of each cycle.
- All the ingredients are placed in one tube.
- The experimenter sets the machine to operate within a defined temperature range and number of cycles.

**Figure 18.6**
The sequential process of denaturing-annealing-synthesis is then repeated for many cycles.

A typical PCR run is likely to involve 20 to 30 cycles of replication.
- This takes a few hours to complete.
- After 20 cycles, a target DNA sequence will increase $2^{20}$-fold (~ 1 million-fold).
- After 30 cycles, a target DNA sequence will increase $2^{30}$-fold (~ 1 billion-fold).
<table>
<thead>
<tr>
<th>Activity</th>
<th>Cellular Replication</th>
<th>PCR</th>
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<tbody>
<tr>
<td>Denaturation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primers</td>
<td></td>
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</tr>
<tr>
<td>Extension</td>
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<td>Number of copies produced</td>
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<tr>
<td>Size of region copied</td>
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</tr>
<tr>
<td>Ingredients</td>
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</tr>
<tr>
<td>Purpose</td>
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Animations
DNA replication is the process in which one double-stranded DNA molecule is used to create two double-stranded molecules with identical DNA sequences.
DNA replication begins at a specific point in the DNA molecule called the origin of replication site.
DNA replication begins when helicase unwinds a segment of the DNA and breaks the hydrogen bonds between the two complementary strands of DNA.
Although mistakes can happen during DNA replication, they are extraordinarily rare. A key reason for this is the proofreading function of DNA polymerase.
The ends of chromosomes contain regions referred to as telomeres. These telomeric regions consist of telomeric repeat sequences.
The polymerase chain reaction is a method for making many copies of a specific segment of DNA, starting with a very small amount.