



Genetics

Subject : Genetics

Lec no : 4

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وَقُلْ رَبِّ زِدْنِي عِلْمًا

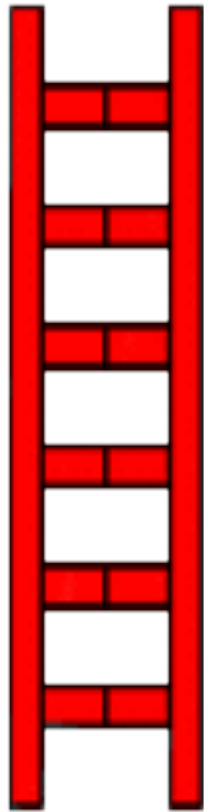
Replication

→ synthesis of DNA (DNA ↓ copy بعمل)

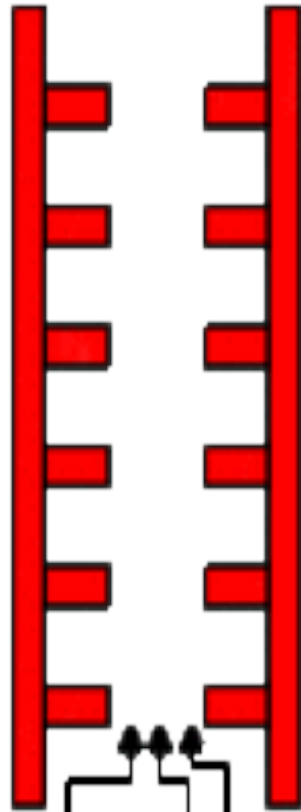
• Replication overview:

- Double-stranded DNA unwinds.
- The junction of the unwound molecules is a replication fork.
- A new strand is synthesized according to base pairing rule with the parent strand.
- Two molecules of DNA are synthesized (daughters), each has one new and one old DNA strand.
- Replication is **bidirectional**: this means that the replication forks move in both direction away from the origin.

1

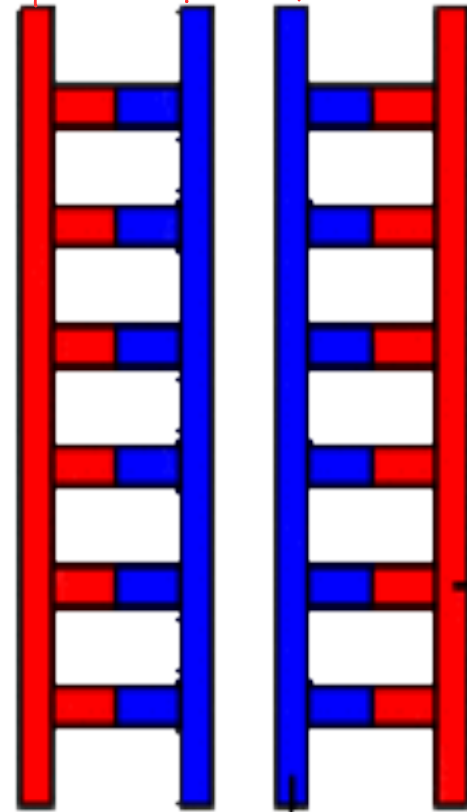


2



3

new strand
old strand
new strand
old strand



Old

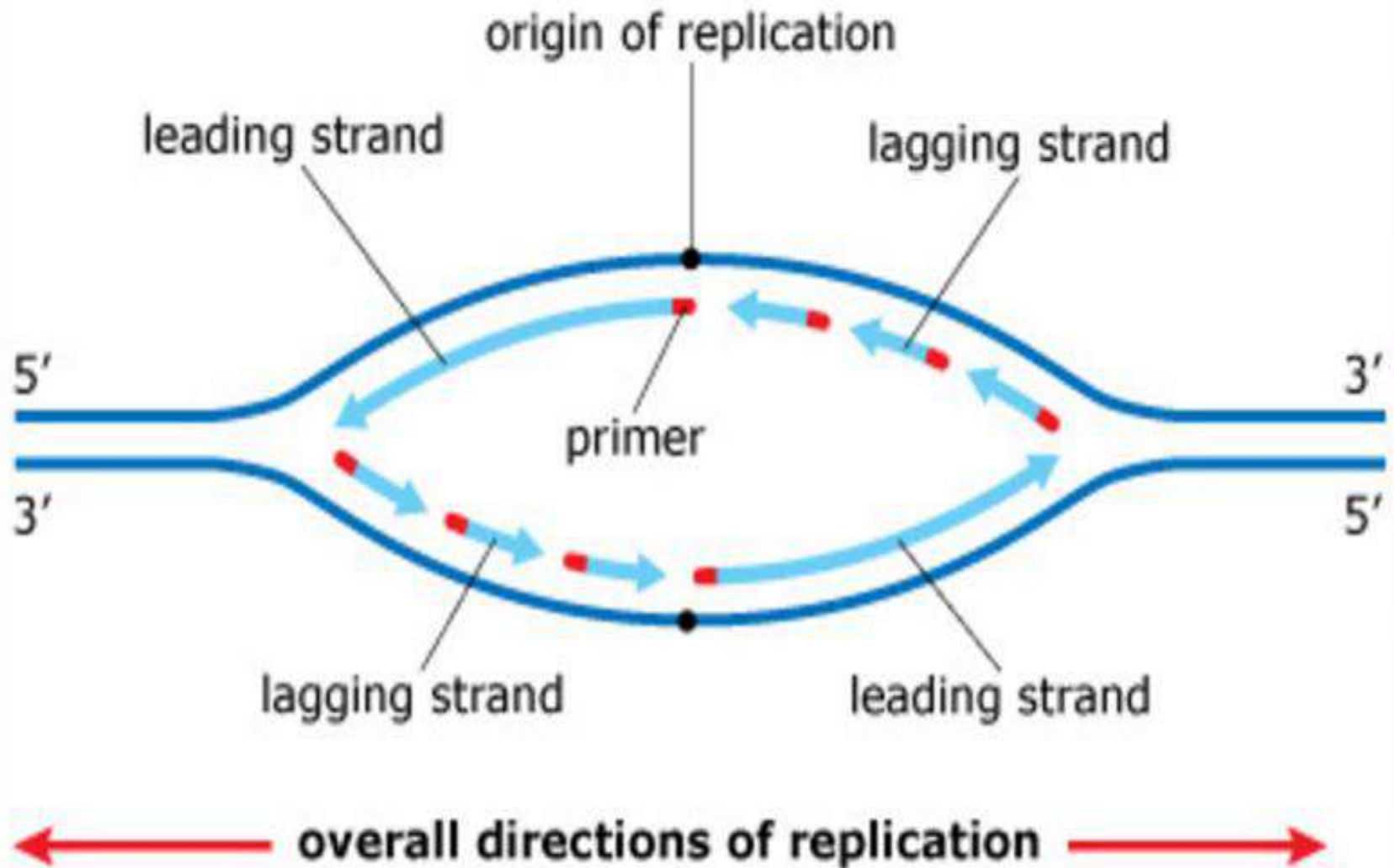
New

New Bases

2 molecules ← molecule من هذا 1
 ال separation (منق) **denaturation** فصل
 ل 2 strands مع
 مع 2 strands مع

كأول شيء لازم فصل
 معك أنه في strand يمكن ان تعمل
 strand مع 2 strands مع
 bases pairing rule

Base pairing rule : with T: the purine adenine (A) always pairs with the pyrimidine thymine (T) C with G: the pyrimidine cytosine (C) always pairs with the purine guanine (G)



* واتجاه فتح **bidirectional** ← replication forks

يمتد وفعال في نفس الوقت

من عند الفتح في **origin of replication** يكون الفتح في الاتجاهين.

من replication fork من جهتي اليمين واليسار

❖ Replication

أصل molecule إلى strand's ← وأبني نام strand ← new strand

- The **synthesis of DNA**. It is the **copying and transformation** of genetic information found in DNA **to daughter cells**. It occurs during the **S phase** of cell cycle.

DNA replication synthesis كما يحصل فيها

القسم / الجزء القديم

تحتي تأتي من انه نضج genetic material من خلال
old strand molecule القديم - تصنعلي (A) strand الجوده تكون نفس
strand القديم التي كانت مرتبطة معها
حافظت على old strand وبنيت اماها
new strand

- DNA replication is **Semiconservative**:
 - During DNA replication the old strands separate from each other, and every strand acts as a **template** for the formation of new complementary strand according to the **base-pairing rule**.
 - with T: the purine adenine (A) always pairs with the pyrimidine thymine (T)
 - with C: the pyrimidine cytosine (C) always pairs with the purine guanine (G)
 - Semiconservative means that the newly formed two daughters DNA contain **one original old strand** and **one newly formed complementary strand**. **This is important to transfer genetic information in the correct sequence.**

daughter DNA
يكوت من old strand
من molecule الاصل
و new strand معة لها.

old strand تتضمن هذا الشرح

Steps of DNA replication:

• A-Separation of the two DNA strands:

* تبدأ عملية separation من specific DNA sequence
لأن في eukaryotes يكون DNA linear فها يتركز أفضل من الاطراف إلى مناطق sequences محددة هي التي يجب البدء من عندها فصل 2 strands عن بعضها.

1-DNA replication starts at a specific DNA sequence called the **origin of replication**.

In prokaryotes it is single and termed **oriC**.

While in eukaryotes there are multiple origins of replication that contain AT base pairs and

called **autonomous replication**

sequences (ARS).

* في prokaryotes يكون DNA circular وفيه فقط single origin of replication
* في prokaryotes (oriC) single origin

حيث أن أول ما اكتشفنا steps of replication في prokaryotes اكتشفنا في escherichia coli نسميها oriC (وهذا ينطبق على prokaryotes)

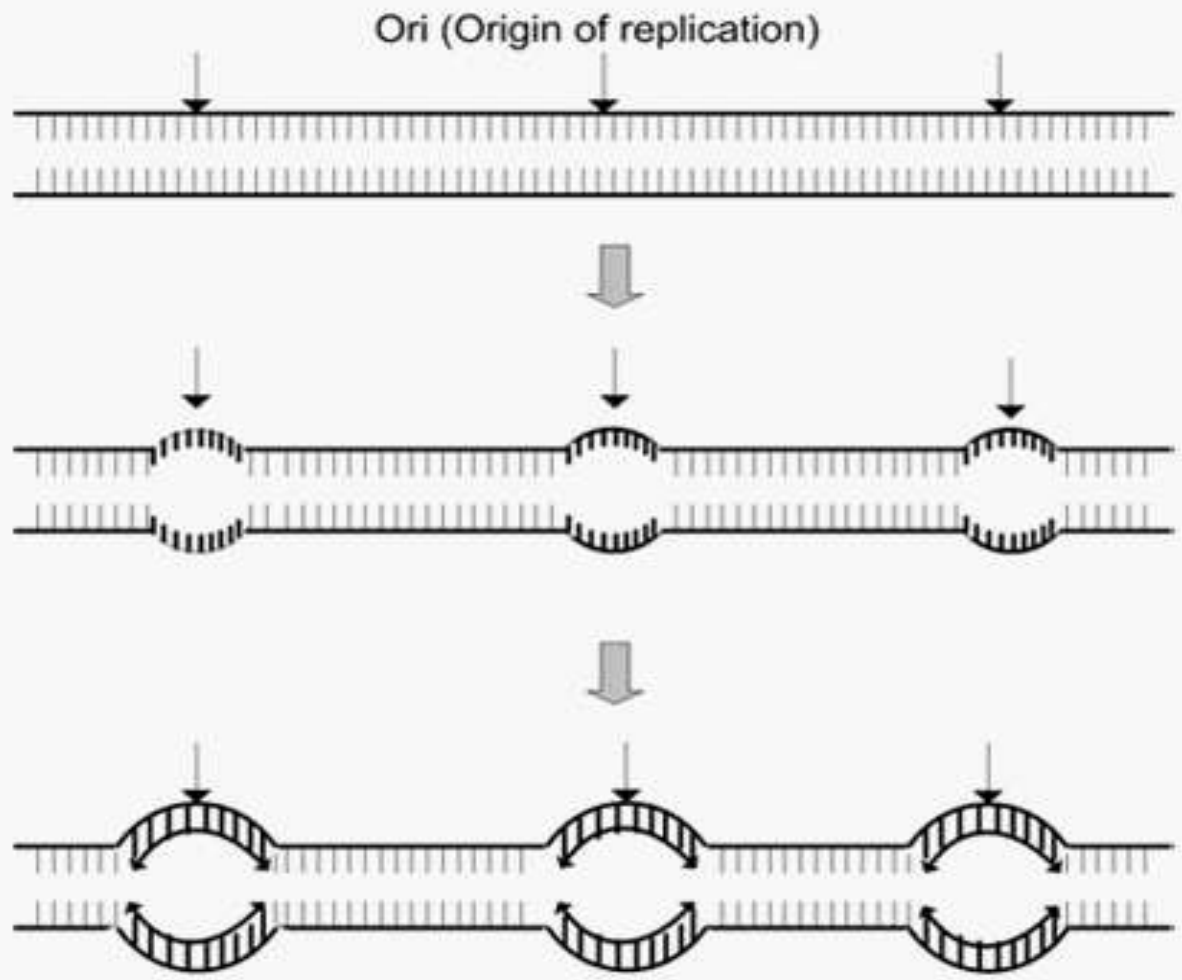
* ما در في الاتن منطقتين فيهن AT base pairs ← centromeres
لـ origins of replication in eukaryotes

Q: لماذا origin of replication في eukaryotes اعظم منها في prokaryotes ؟
لأنك في DNA في eukaryotes أطول وعملية replication تم في phase S وفي phase G ولا يمكن أن تتجاوزه فوجب أن تكرر عملية replication في هذه phase .

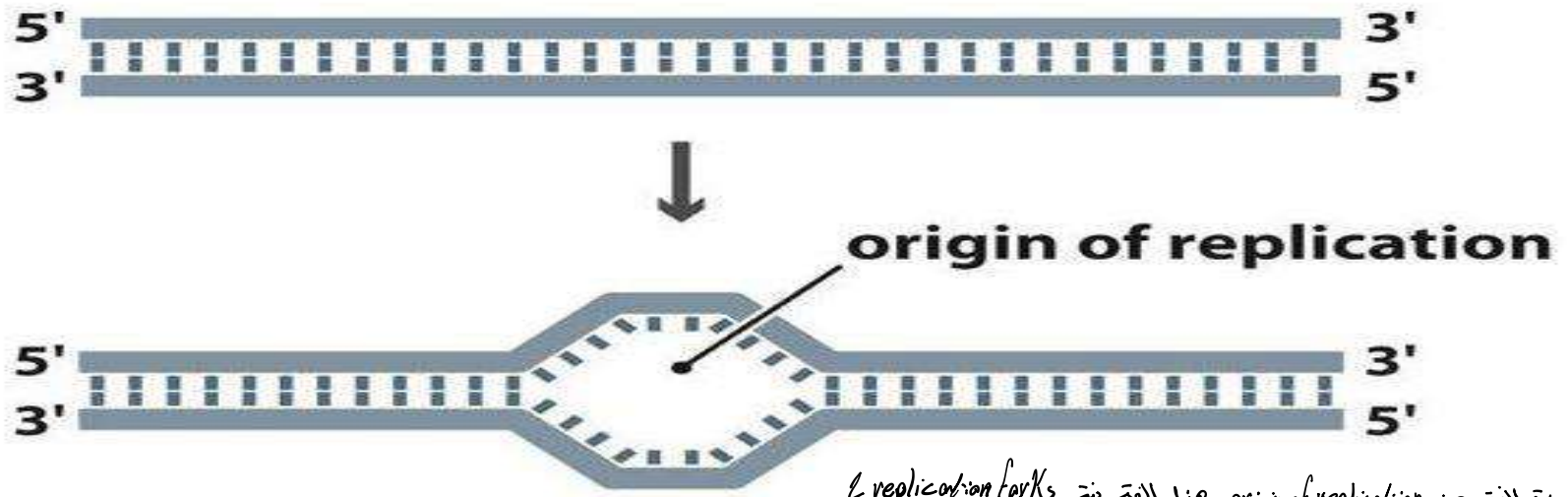
Prokaryote replication

Eukaryotic replication

single origin of replication

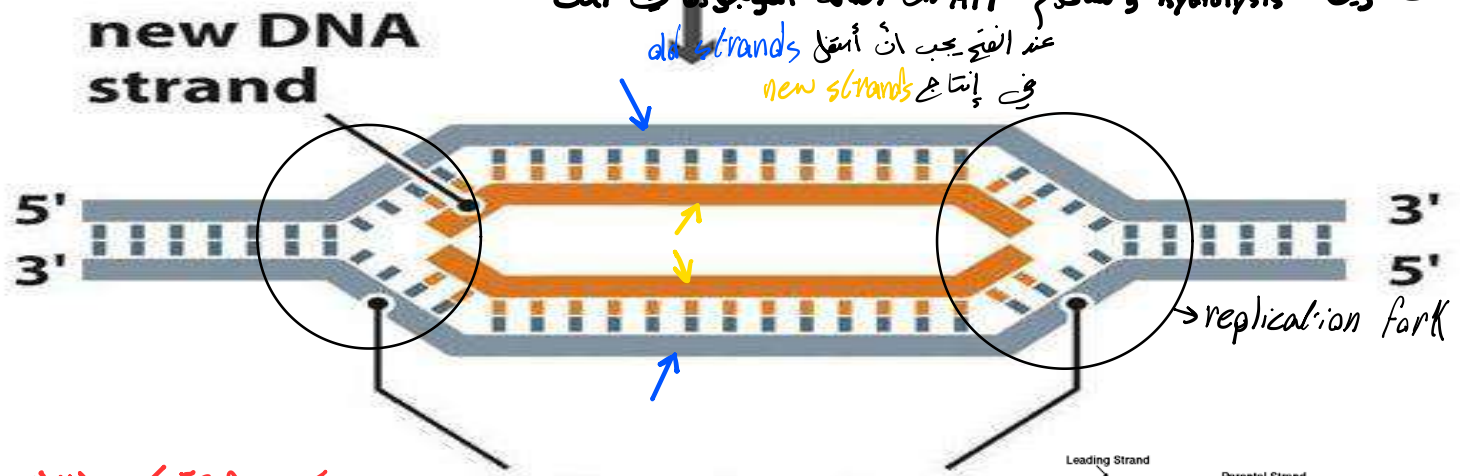


dna.A protein هو الوحدة الذي يتم من origin of replication في very small region
 كعمت طريق hydrolysis وتستخدم ATP من الطاقة الموجودة في cell
 helicase enzyme هو الذي يجعل الفتح
 كعمت طريق hydrolysis وتستخدم ATP من الطاقة الموجودة في cell



* تبدأ عملية الفتح من origin of replication وهذا الفتح ينتج 2 replication forks

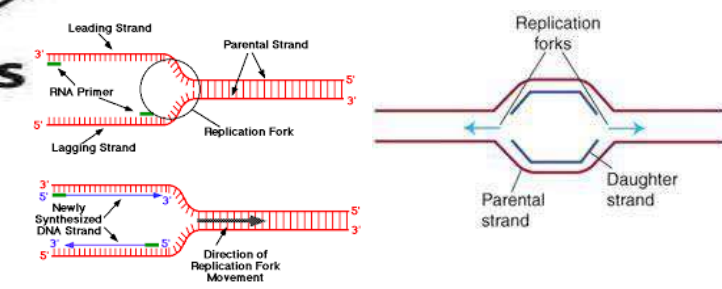
كعمت طريق hydrolysis وتستخدم ATP من الطاقة الموجودة في cell
 عند الفتح يجب أن أُنتقل old strands في إنتاج new strands



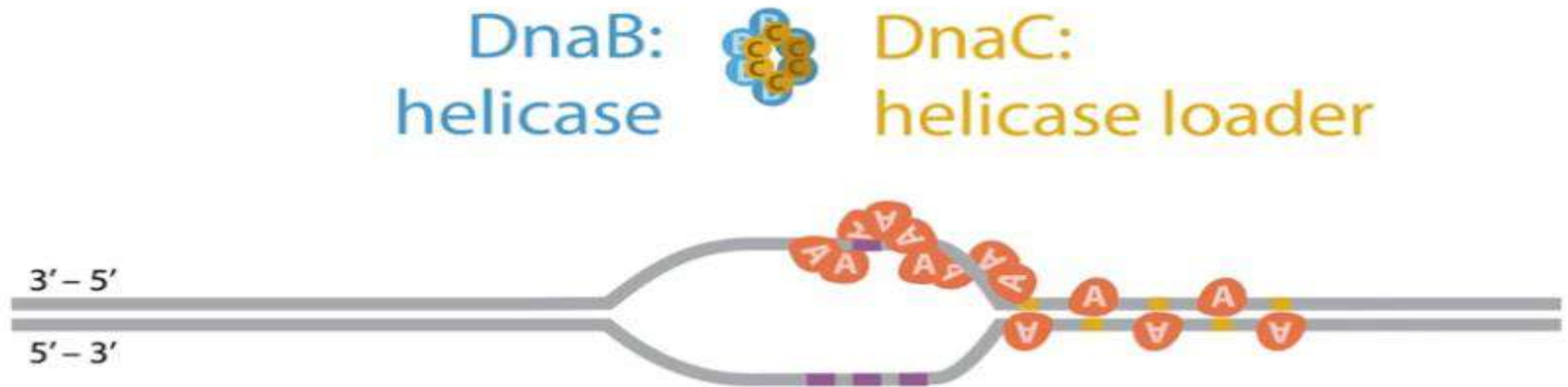
مثل قبال الشوكة = (الانتقاد بين DNA المفرد single strands و DNA الذي لم يفتح بعد double strands)

replication forks

Figure 10.16 Introduction to Genetics (© Garland Science 2012)



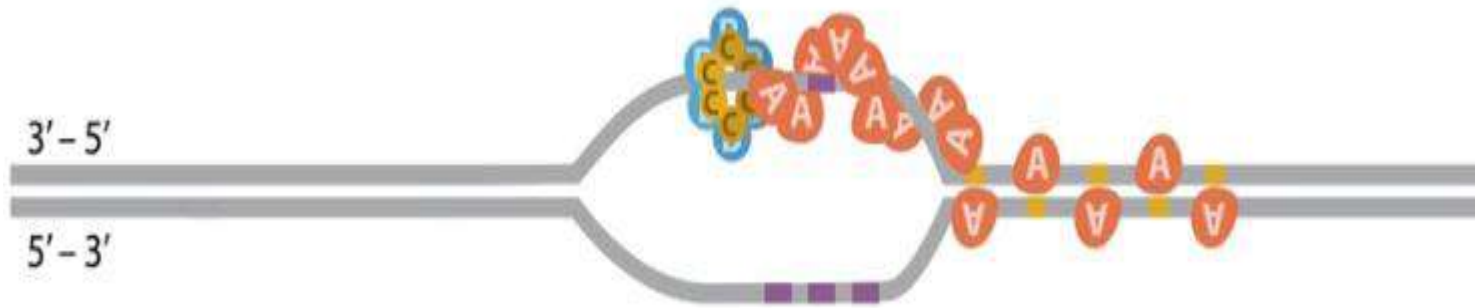
Initiation of DNA Replication in Bacteria



After the **initiator (DnaA)** has bound to **oriC**, the combination of **ssDNA** and DnaA recruits a complex of two proteins:

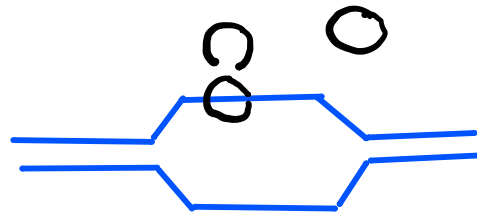
single strand DNA

the **DNA helicase (DnaB)** and **helicase loader (DnaC)**. **Importantly**, binding to the helicase loader inactivates the DNA helicase, preventing it from functioning at inappropriate sites (non origin regions).



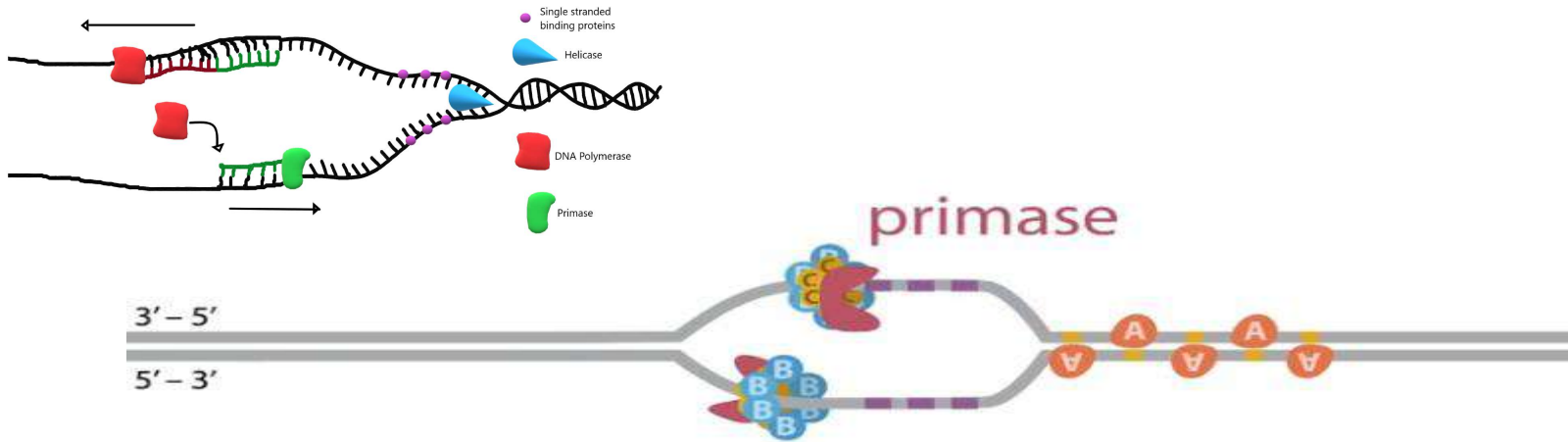
Although the mechanism of loading is not understood in detail, the process requires the opening of the DNA helicase ^{6 subunits} hexameric ring to allow it to encircle the targeted ssDNA

single strand



دنا B helicase
 دنا C helicase loader
 single strand ↓ incurciling
 single strand

Initiation of DNA Replication in Bacteria



DNA primase ← يبين RNA primer وليس DNA primer
 لأن specific substance التي يتقارب معها هي RNA nucleotides (RNA primer)

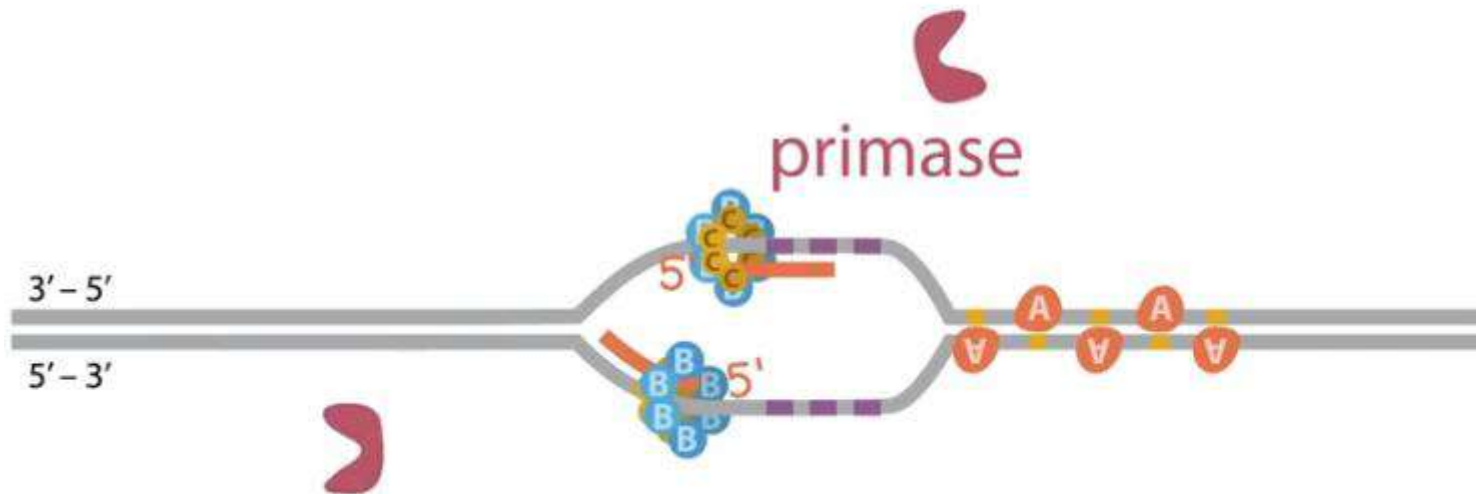
enzyme مسؤول عن تصنيع RNA primer

Helicase recruits DNA primase to the origin DNA, resulting in the synthesis of an RNA primer on each strand of the origin. In addition to generating the primers for the leading DNA strands, this event also causes the release of the helicase loader and, therefore, the activation of the helicase.

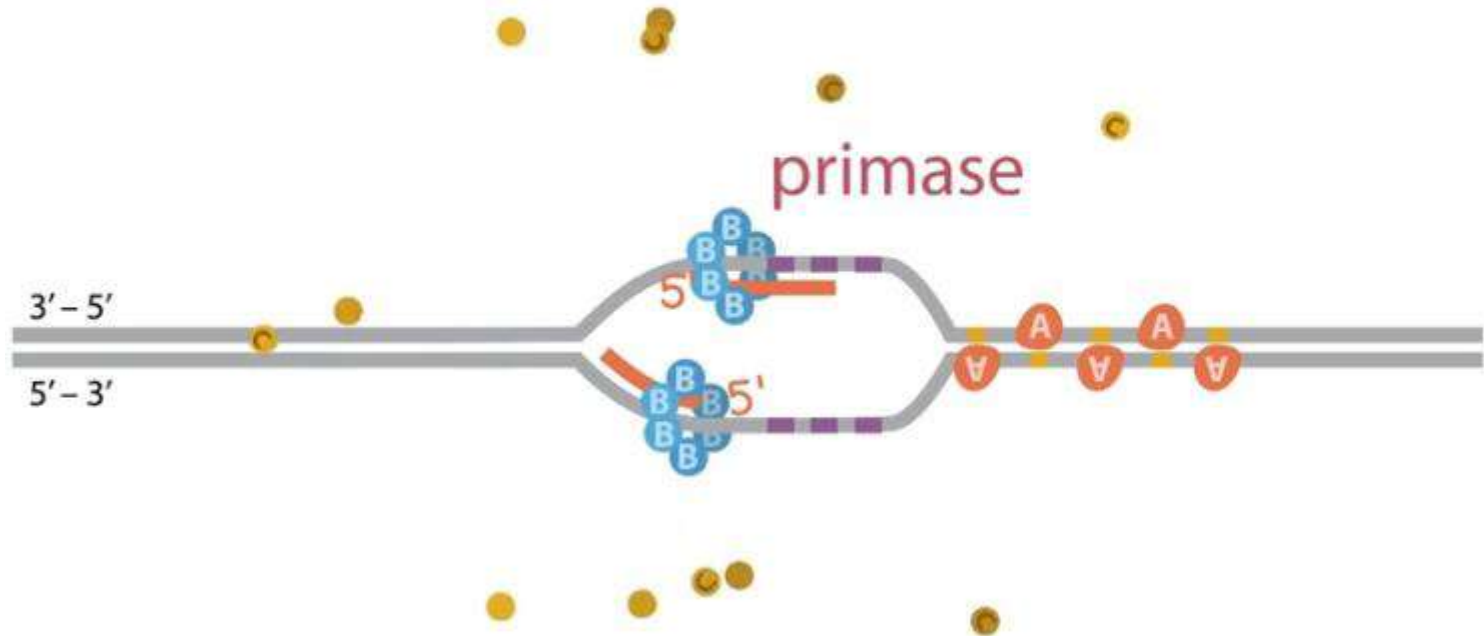
قيادة

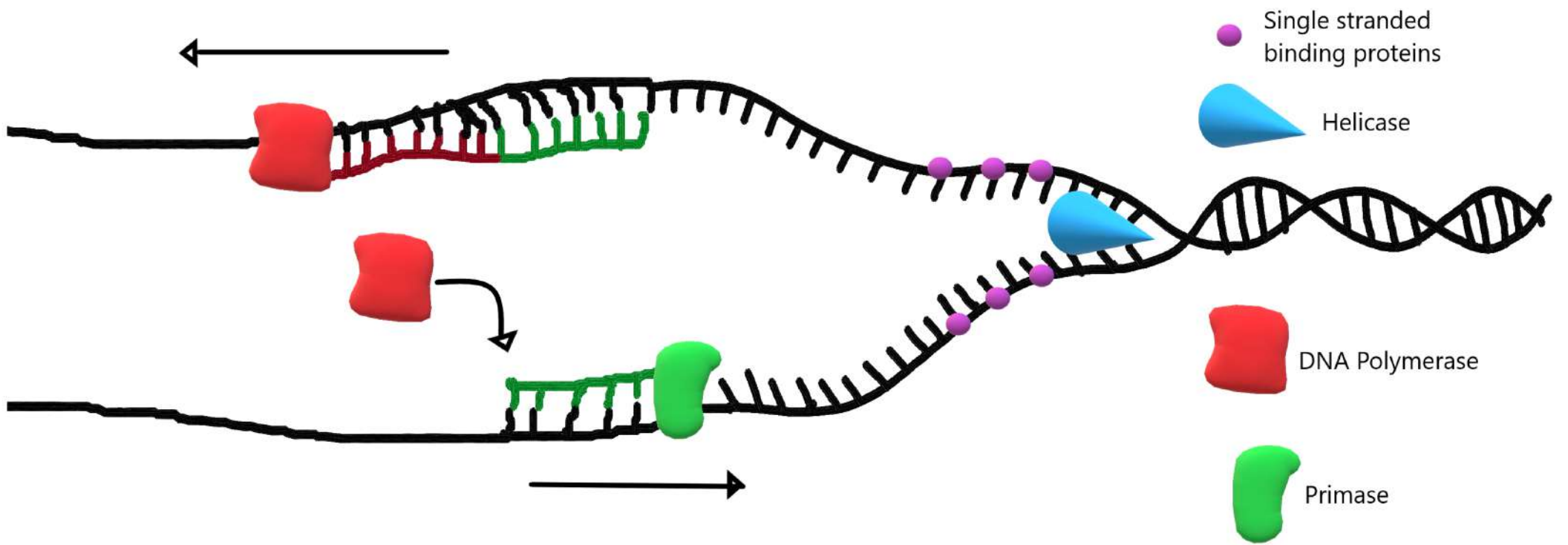
DNA primase synthesis of an RNA primer on each side → release of dnaC helicase loader → activation of the dnaB helicase

Initiation of DNA Replication in Bacteria



Initiation of DNA Replication in Bacteria





3-DNA helicase (dnaB protein) enzyme separates the double helix by breaking the hydrogen bonds between the two DNA strands using energy from ATP hydrolysis.

4-The 2 DNA strands are kept apart (unpaired) by special proteins known as single strand DNA binding proteins (SSB), which binds tightly to each separated strands preventing them from rejoining & protect the single stranded DNA from nucleases that cleave it.

← nucleases enzyme لما يشوف أي single strand DNA molecule بتكسر
← SSB يمنع single strands من الازدياد مرة اخرى.
← بيحوي single strands من nucleases

كل ما الى يانها بالمنطق

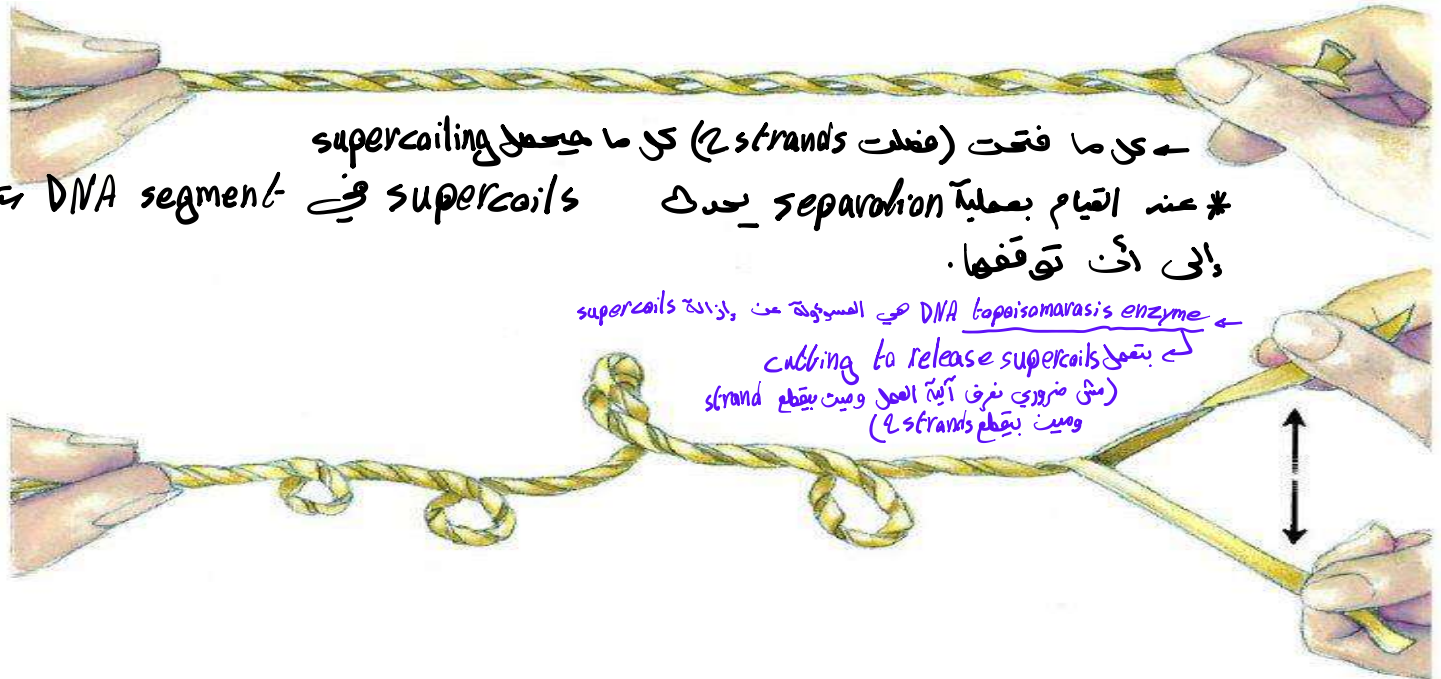
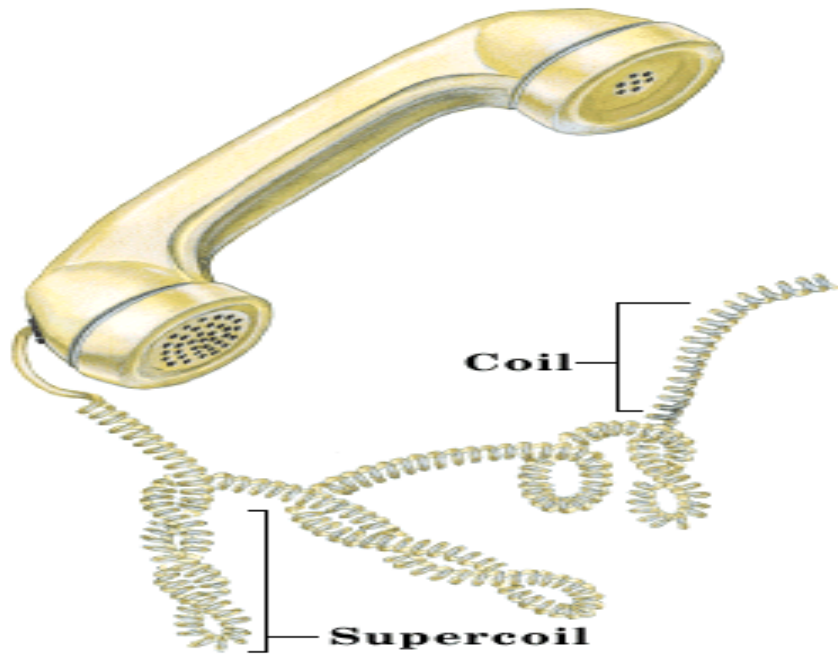
5-Prepriming complex: formed from **dnaA protein**, **dnaC protein**, **SSB proteins**, and **^{dna B helicase} DNA helicases**. This complex is responsible for replication initiation and maintaining the separation of the two DNA strands.

6-DNA Topoisomerases: are responsible for removing supercoils in the helix formed as the 2 strands are separated from each other, this creates coils in front of the separated part (supercoils) which prevents further separation of the helix. Topoisomerases have both **nuclease** (strand cutting) and **ligase** (strand resealing) activities. Topoisomerases make transient cut (in the phosphodiester bond) in one strand (**topoisomerase I**) or both stands (**topoisomerase II**).

مهم ضروري نعرف ميت. يعمل cutting ↓ one strand. يعمل 2 strands فقط نعرف انه يوجد 2 types

topoisomerase I

topoisomerase II



← كل ما فتحت (فضلت 2 strands) كل ما يحصل supercoiling
 * عند القيام بعملية separation يدك supercoils في DNA segment تتعيق عملية الفصل
 وإلى أن توقفها.

← DNA topoisomerase enzyme هي المسؤولة عن إزالة supercoils
 ← لعملية cutting to release supercoils
 (مش ضروري نرفق آلية العمل وميت بقطع strand
 وميت بقطع 2 strands)

الدكتورة لم تتكلم عن الغير مخطأ

بما أنها أحد أنواع *topoisomerase* ← وإذن يساعد في إزالة *supercoils*

7-DNA gyrase, a Type II topoisomerase found in bacteria and plants, has the unusual property of being able to introduce negative supercoils into relaxed circular DNA using energy from the hydrolysis of ATP. This facilitates the future replication of DNA because the negative supercoils neutralize the positive supercoils introduced during opening of the double helix. It also aids in the transient strand separation required during transcription.

8- Now each relaxed single strand acts as a template to direct the synthesis of a new daughter DNA strand.

مكتوبه

Drugs تثبند topoisomerase ← وبالتالي لن تتمكن الخلية من عمل replication لأنها لن تستطيع عمل separation

وبالتالي فإن البكتيريا تموت.

❖ Clinical significance:

- **Quinolones** antimicrobial drugs e.g. nalidixic acid (Negram) act by inhibiting bacterial gyrase preventing bacterial replication and transcription.
inhibit topoisomerase ← يعني inhibit gyrase
- **Anticancer agents**, such as etoposide, target human topoisomerase II.

* يقتل cancer cells عن طريق منع حدوث replication DNA → إتلافها

