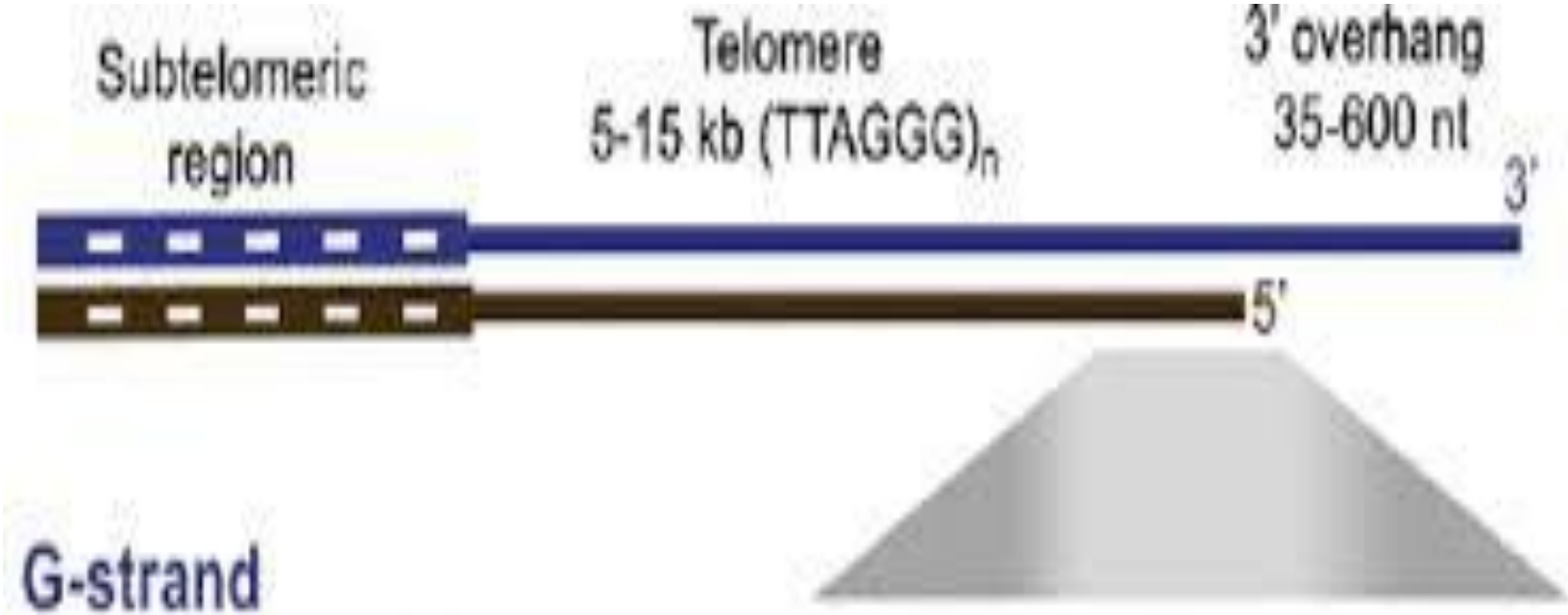
Telomeres and Telomerases

The end replication problem

By
Dr. Walaa Bayoumie El Gazzar

Telomeres and Telomerases

- **Telomeres:** Telomeres are complexes of **noncoding DNA plus proteins** located at the ends of linear chromosomes.
- Its name is derived from the Greek nouns telos "end" and meros "part".
- Their DNA consists of thousands of repeats of a six-nucleotide sequence 5`-**TTAGGG -3`** at the **3`** end of each DNA strand.
- The **3`** end overhangs the 5`end by a few hundred nucleotides long. The overhanging end folds back on itself and binds proteins that protect it from recombination.
- They **maintain the structural integrity of the chromosome**, **preventing attack by nucleases**, and **allow repair systems to distinguish a true end from a break in dsDNA**.



G-strand

TTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAGGGTTAG 3'
AATCCCAATCCCAATC 5'

C-strand

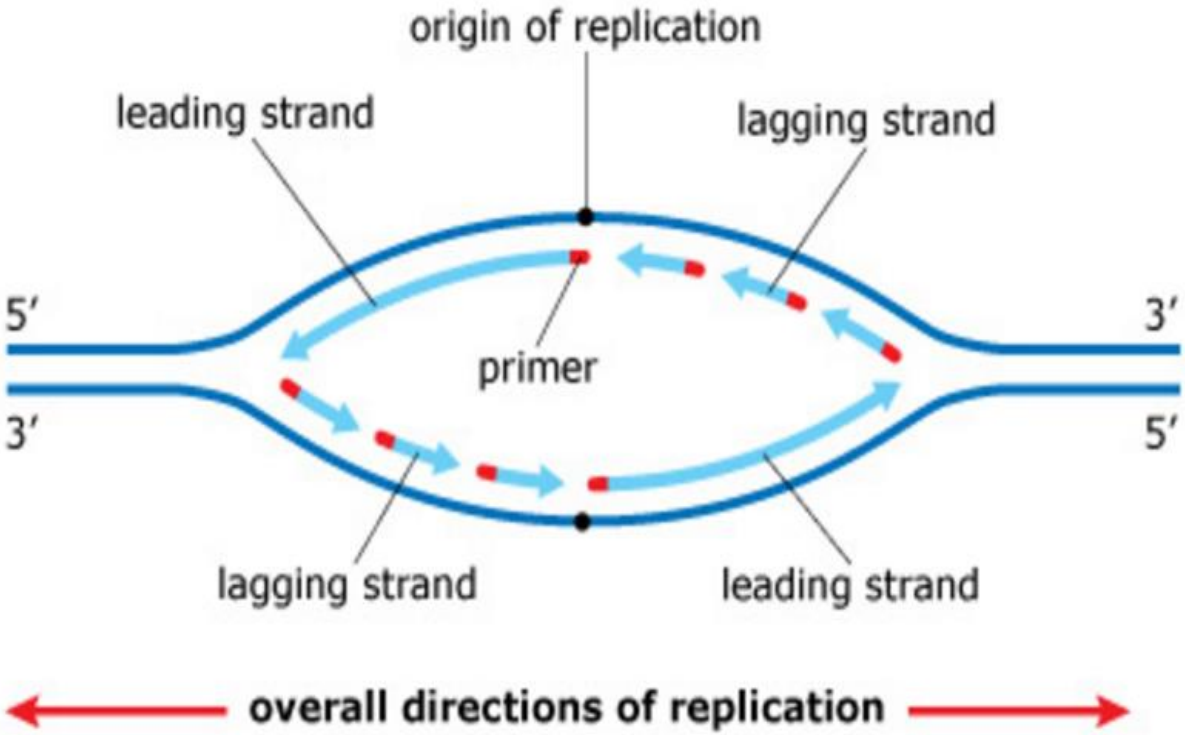
Telomere shortening:

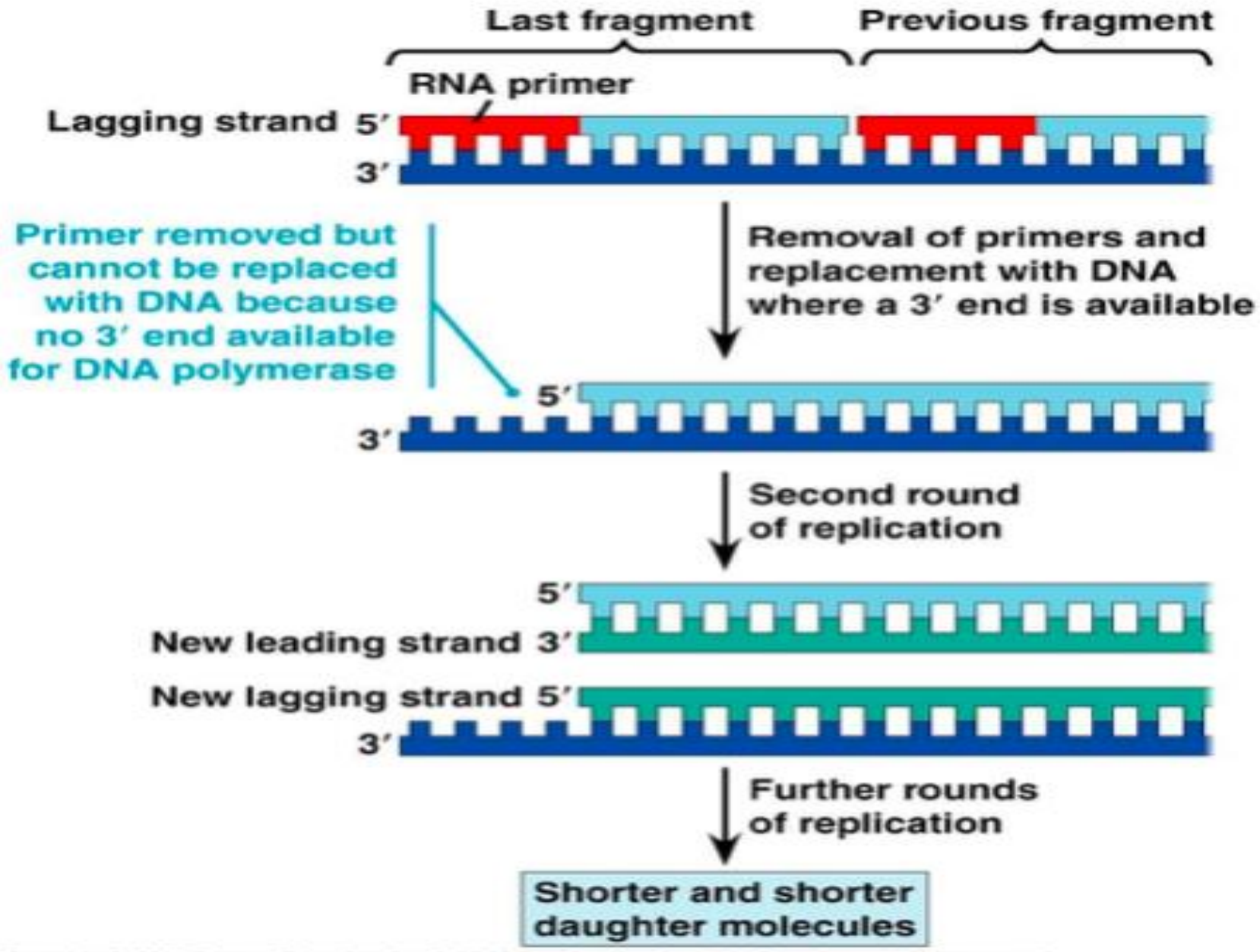
- Eukaryotic cells face a special problem in replicating the ends of their linear DNA molecules. Following removal of the RNA primer **from the extreme 5'-end of the lagging strand**, there is no way to fill in the remaining gap with DNA.

- Consequently, in most normal human somatic cells, **telomeres shorten** with each successive cell division **which may not be a problem after a few cell cycles because telomeres do not contain expressible genes.**

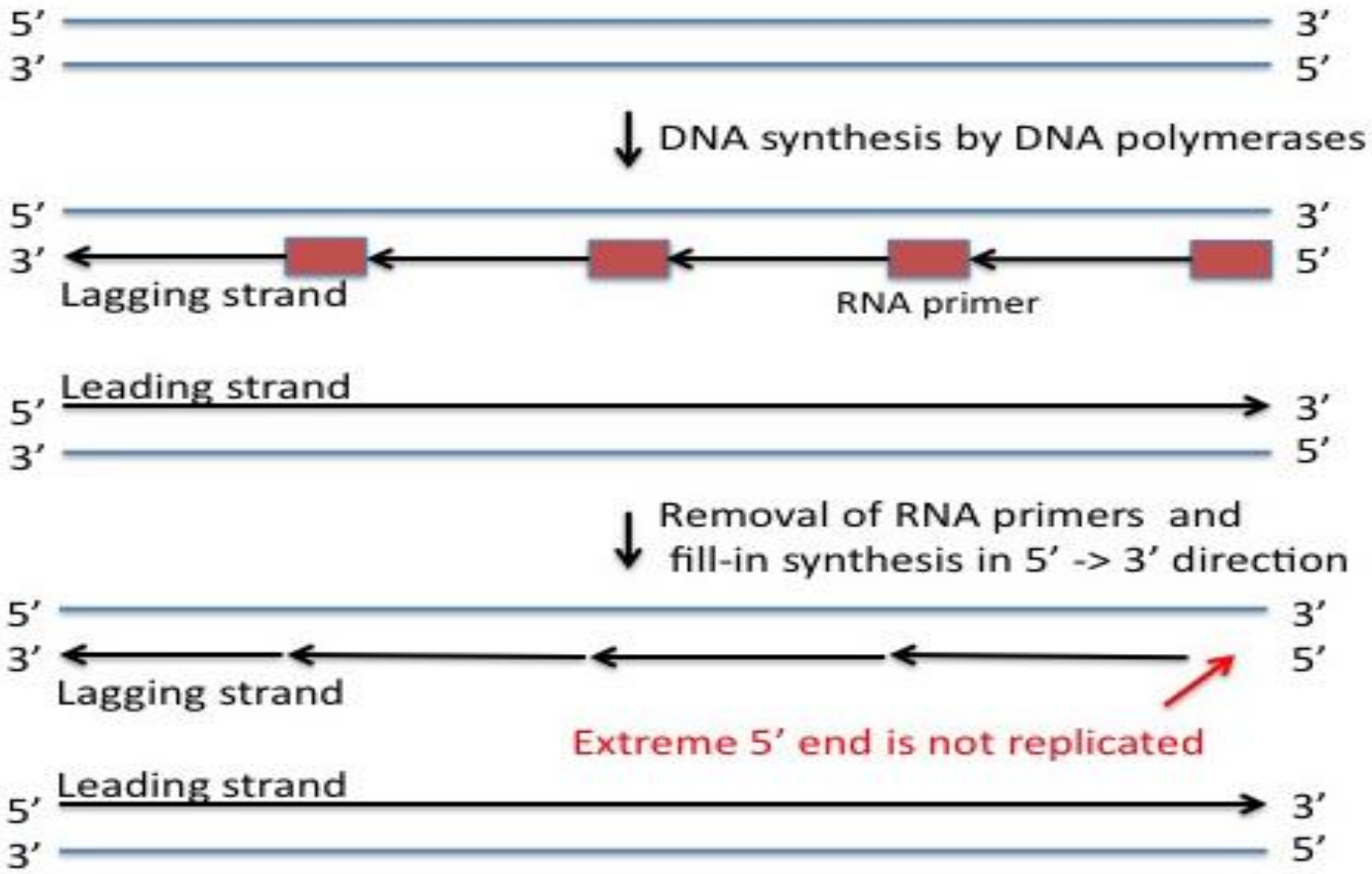
- Once telomeres are shortened beyond some critical length, the cell is no longer able to divide and is said to be **senescent**.

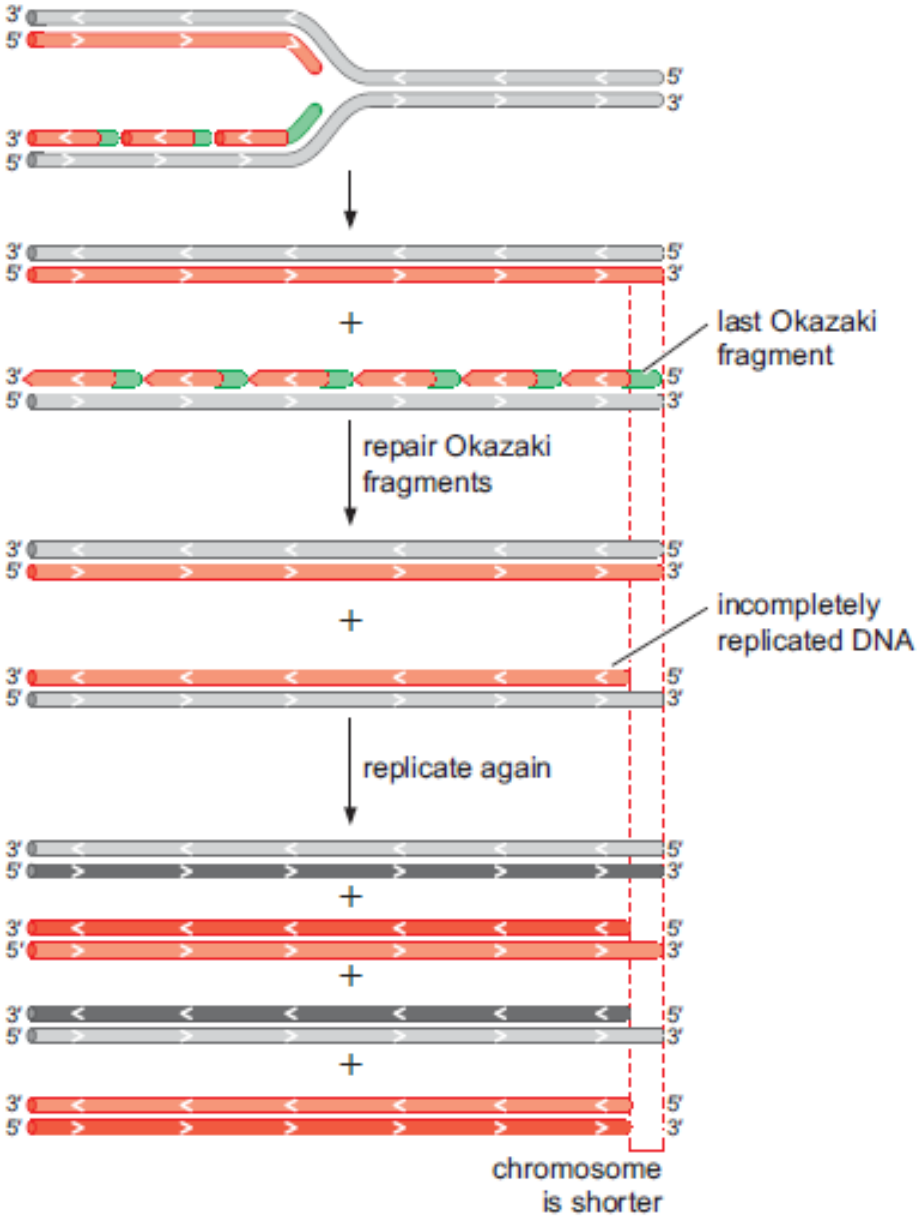
- In germ cells and other stem cells, as well as in cancer cells, telomeres do not shorten and the cells do not senesce. **This is a result of the presence of a ribonucleoprotein, telomerase, which maintains telomeric length in these cells. Cells that no longer divide or will divide only a few number of times do not express telomerase**


origin of replication
leading strand
lagging strand
5′
3′
primer
3′
5′
lagging strand
leading strand
overall directions of replication


Last fragment
Previous fragment
RNA primer
Lagging strand 5′
3′
Primer removed but cannot be replaced with DNA because no 3′ end available for DNA polymerase
Removal of primers and replacement with DNA where a 3′ end is available
5′
3′
Second round of replication
5′
New leading strand 3′
New lagging strand 5′
3′
Further rounds of replication
Shorter and shorter daughter molecules

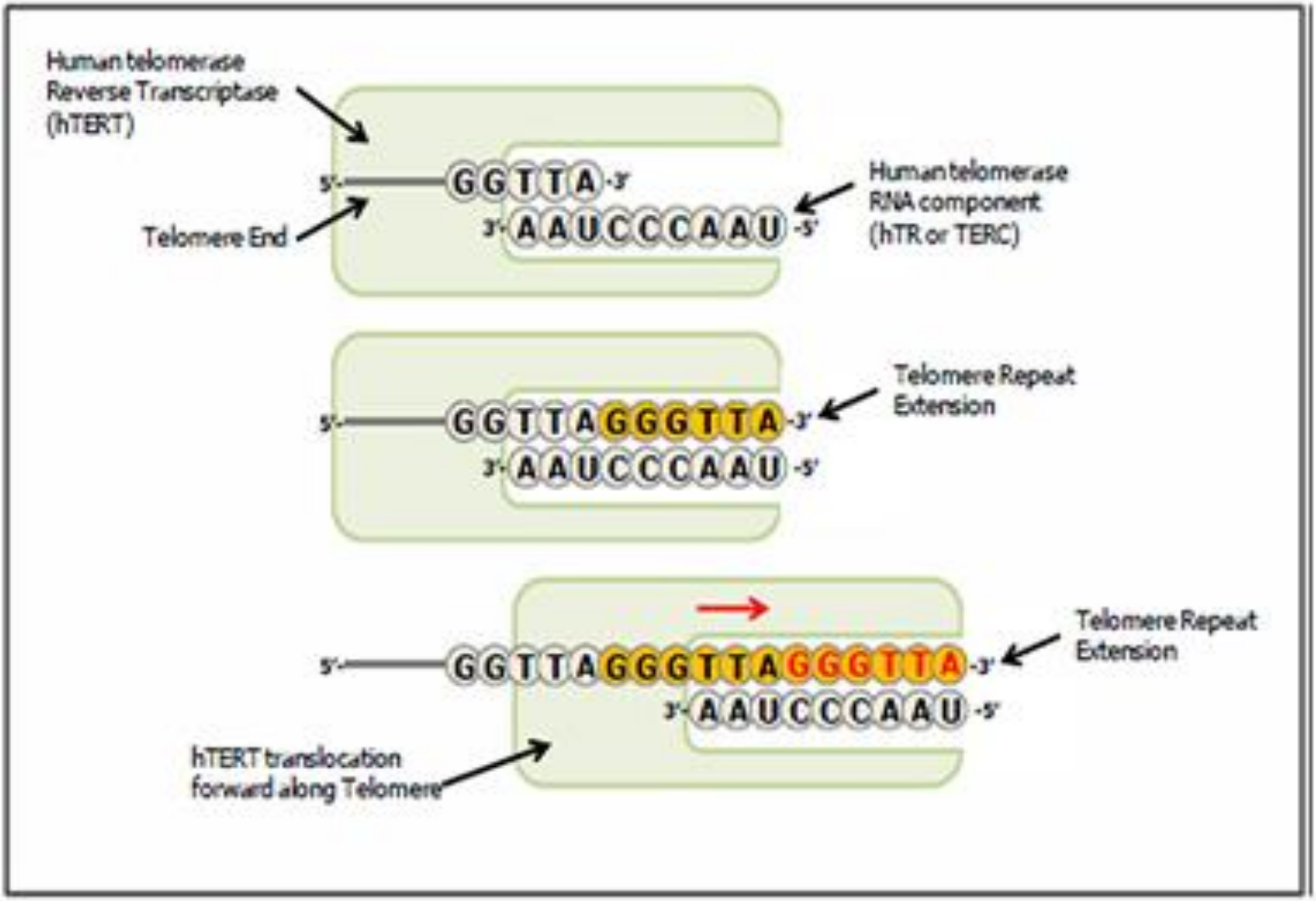
END REPLICATION PROBLEM




3′
5′
5′
3′
last Okazaki fragment
repair Okazaki fragments
incompletely replicated DNA
replicate again
chromosome is shorter

Telomerase:

- Telomerase is a **reverse transcriptase** (uses an internal RNA strand as a template for synthesis of a complementary DNA strand).
- Its activity depends on the presence of an RNA molecule in its structure, **which is complementary to the TTAGGG repeat.**
- Telomerase recognizes the single stranded 3` terminus and uses its RNA molecule as a template to elongate the parental strand then this parental strand is used as a template for synthesis of the telomere of the lagging strand


Human telomerase
Reverse Transcriptase
(hTERT)
5'-
GGTTA-3'
3'-AAUCCCAAU-5'
Telomere End
Human telomerase
RNA component
(hTR or TERC)
Telomere Repeat
Extension
5'-
GGTTAGGGTTA-3'
3'-AAUCCCAAU-5'
Telomere Repeat
Extension
5'-
GGTTAGGGTTAGGGTTA-3'
3'-AAUCCCAAU-5'
hTERT translocation
forward along Telomere