NAIST® Research Highlights

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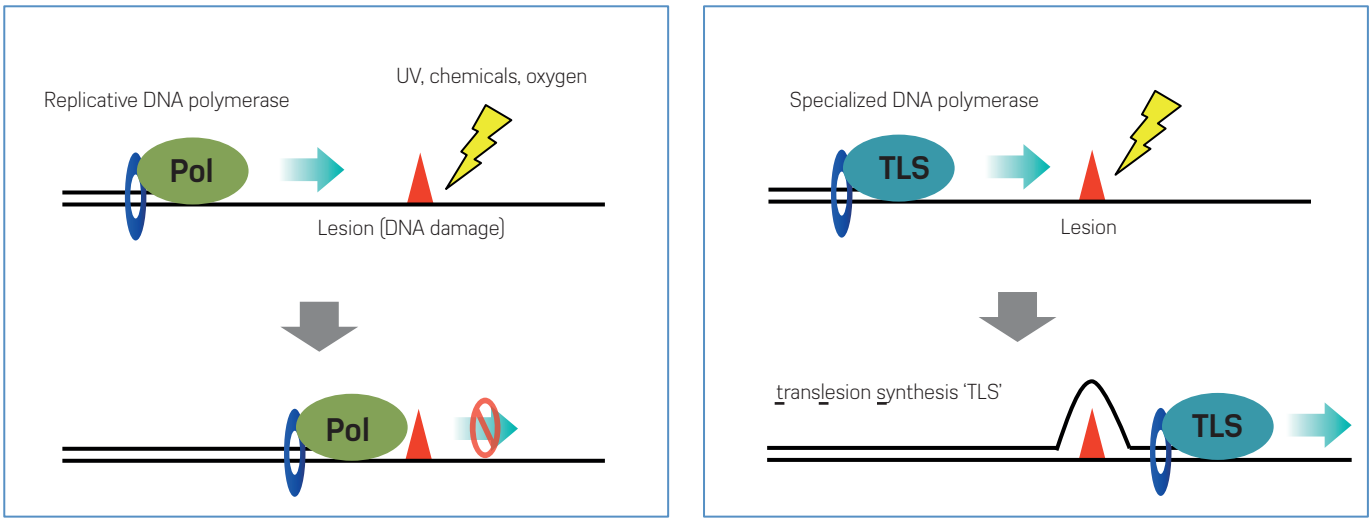

After a replicative DNA polymerase stalls at a lesion site (left), a specialized polymerase for translesion synthesis (TLS) helps overcome the DNA damage (right).

Genetics

Repair enzyme also reboots genome copying

DNA polymerase IV enzyme involved in damage tolerance also aids in DNA synthesis

A special bacterial enzyme involved in repairing the genome also helps restart DNA replication after the process has stalled[1]. The finding, from researchers at NAIST in Japan, could shed light on the source of genetic mutations — a major cause of cancer and other age-related diseases.

When the cell is exposed to a dangerous chemical, sometimes a piece of DNA will form a bond with the chemical agent. This creates what is known as a DNA lesion. These lesions will block the genetic copying machinery, but fortunately the cell has a class of enzymes to deal with these kinds of obstruction.

Humans and other eukaryotes use one set of enzymes, while bacteria and other prokaryotes use another. Through a process known as translesional synthesis (TLS), these specialized enzymes help overcome DNA lesions so that the standard gene copying enzyme can continue its normal function.

In the rod-shaped bacterium *Escherichia coli*, an enzyme called DNA polymerase IV was not thought to be involved in TLS for major lesions (see figure). However, a team led by Hisaji Maki at NAIST, along with collaborators in France and the United States, has now discovered multiple new functions of this enzyme.

> **"Polymerase IV can transiently and efficiently work in the replication fork, instead of the normal type of DNA polymerase."**

The researchers exposed a circular piece of *E. coli* DNA to a compound found in coal tar that forms bonds with DNA. They then recreated the entire DNA copying process, and — in a first — watched what polymerase IV did at the replication fork, the junction where the double-stranded DNA splits apart into two single strands during replication.

"Unexpectedly, we observed that polymerase IV entered into the replication machinery very effectively," says Asako Furukohri, a biochemist at NAIST and one of the co-first authors of the study.

Polymerase IV not only aided with gene synthesis over the damaged DNA — it helped with the entire process of resuming gene copying. "Polymerase IV can transiently and efficiently work in the replication fork, instead of the normal type of DNA polymerase," Furukohri says. "Our finding suggests the possibility that polymerase IV may play some role in genomic DNA replication." Polymerase IV is known to make more copying mistakes than standard replication enzymes, and the mutations it introduces have been linked to drug resistance in bacteria. The human equivalent of polymerase IV has also been implicated in different forms of cancer. Knowing the role of polymerase IV in genomic replication is thus "an important issue," says Furukohri, because it could reveal the genomic triggers of mutation-driven diseases.

Reference

1. Ikeda, M., Furukohri, A., Philippin, G., Loechler, E., Akiyama, M.T. *et al.* DNA polymerase IV mediates efficient and quick recovery of replication forks stalled at N^2-dG adducts. *Nucleic Acids Research* **42,** 8461–8672 (2014).

More infornmation about the group's research can be found at the Microbial Molecular Genetics Laboratory webpage:
http://bsw3.naist.jp/eng/courses/courses301.html